Iminosugars as Glucosylceramide Processing Enzymes Inhibitors: Design, Synthesis and Evaluation

PROEFSCHRIFT

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Bing Liu

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1 General Introduction

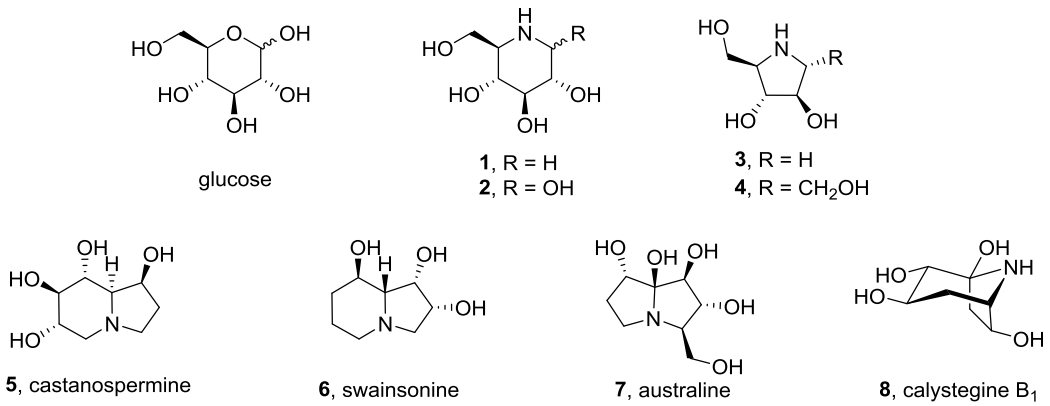
Introduction

Iminosugars, carbohydrate mimetics that feature a nitrogen atom substituting the furanose/pyranose ring oxygen in the parent sugar they emulate (Figure 1), are widely spread in nature.[1] Iminosugars are highly sought-after commodities because of their potential to inhibit glycoprocessing enzymes, with potential application in buffering diet polysaccharide degradation and in modulating glycoconjugate metabolism.[2] Today, iminosugars are in clinical use, or are considered as suitable leads for clinical development, for a range of human disorders including lysosomal storage disorders, type 2 diabetes, cancer, bacterial infections and viral infections.[3]

Natural occurrence and biological activities

The naturally occurring iminosugars can be classified in several structural classes, including pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes (Figure 1). The first iminosugar discovered from natural sources is nojirimycin (NJ, **2**), which was isolated in 1966.[4] Nojirimycin is a close glucopyranose analogue that only differs from glucose in the nature of the heteroatom within the ring: nitrogen instead of oxygen (Figure 1). Nojirimycin is a potent inhibitor of various glucosidases, however the highly acid-labile hemi-aminal moiety that characterizes nojirimycin also renders the compound relatively unstable in physiological conditions. 1-Deoxynojirimycin (DNJ, **1**) is a comparably much more stable compound that however possesses very similar biological properties. DNJ was synthesized in 1968[5] and isolated from plants in 1976,[6] and is a potent inhibitor of a large number of α-glucosidases as well as β-glucosidases.[7, 8] 1,4-Dideoxy-1,4-imino-D-arabinitol (DAB, **3**), and 2*R*,5*R*-dihydroxymethyl-3*R*,4*R*-dihydroxy-pyrrolidine (DMDP, **4**) are representative examples of naturally occurring pyrrolidine iminosugars and have been isolated from tropical and temperate plants.[9] Pyrrolidine **3** is a potent inhibitor of α-glucosidases, β-glucosidases and α-mannosidases,[10] and its close structural analogue **4** inhibits a wide range of glycosidases as well.[11]

***Figure 1**: Structures of different classes of iminosugars*



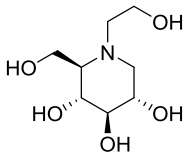
Bicyclic iminosugars abound in nature as well and are also often quite potent glycosidase inhibitors. The archetypal indolizidine iminosugar, castanospermine (**5**), isolated from Leguminosae, is an inhibitor of both α-glucosidases and β-glucosidases, thus resembling the activity profile of DNJ **1**.[12-16] Swainsoine (**6**), isolated from leaves, stems and seeds of various plants,[17, 18] is another widely studied indolizidine iminosugar and is a potent α-mannosidase

inhibitor.[19] A relevant pyrrolizidine iminosugar comprises australine (**7**), an inhibitor of both α-glucosidases and β-glucosidases that is found in *Leguminosae* seeds and leaves.[20] Calystegine B_1 (**8**) is a tetra-hydroxyl nortropanes alkaloids isolated from *Convolvulaceae*, and found to be a strong inhibitor of glucocerebrosidase.[21]

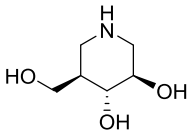
Clinical relevance

Iminosugars have long been regarded as promising starting points for drug development and today several iminosugars are in clinical use for the treatment of a number of human diseases. One early example of the therapeutic use of iminosugar-containing material comprises the application of mulberry leaves and bark, in Asia many years ago, for the treatment of diabetes. Several decades ago, both NJ and DNJ were isolated from mulberry leaves, and subsequently shown to inhibit of intestinal digestive glycosidases, thus affecting the digestion and absorption of carbohydrates. On the basis of DNJ, the antidiabetic agent, Miglitol (**9**), which has a better activity and selectivity compared with DNJ, was developed. Today, Miglitol is in clinical use for the oral treatment of type II diabetes.

***Figure 2**: Structures of Miglitol and isofagomine*



9, Miglitol



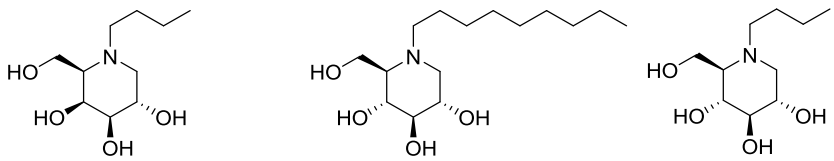
10, isofagomine

Another glycoprocessing enzyme associated with diabetes is hepatic glycogen phosphorylase. Hepatic glucose levels are increased in type II diabetes patients[22] and it is thought that buffering glucose levels can be effected through inhibition of hepatic glycogen phosphorylase. DAB (**3**, Figure 1) proved to be a potent hepatic glycogen phosphorylase inhibitor and by this virtue lowers gluconeogenesis from hepatic glycogen.[23] Isofagomine (**10**) is another potent hepatic glycogen phosphorylase inhibitor, and is also able to partially prevent gluconeogenesis in animal models.[24]

Perhaps the most successful application of iminosugars in therapy is found in the area of lysosomal storage disorders, in particular Gaucher disease. Lysosomal storage disorders (LSD) comprise about 50 inherited diseases, each caused by inherited, genetic mutations in particular lysosomal proteins, most commonly hydrolytic enzymes. Gaucher disease is a relevant example both for the work described in this Thesis and for LSDs in general: it is

perhaps the best studied member of the LSD family and several therapeutic intervention strategies are in clinical practice or are in clinical development. Gaucher disease is characterized by partial or complete (depending on the nature of the mutation) dysfunctional lysosomal glucosylceramidase (GBA1). GBA1 hydrolyses the interglycosidic linkage in glucosylceramide and (partial) deficiency in GBA1 leads to accumulation of this substrate as well as the unusual lysolipid, glucosylsphingosine. Gaucher pathology likely is partially caused by accumulation of these lipids. Gaucher patients (at least those suffering from relatively mild Gaucher as the result of partial, but not complete, impairment in GBA1) can be treated intravenously with recombinant GBA1 in what is termed enzyme replacement therapy (ERT). Alternatively, the enzyme responsible for the synthesis of the primary storage material in Gaucher disease, glucosylceramide synthase (GCS, producing glucosylceramide from UDP-glucose and ceramide) can be partially inhibited by *N*-butyl-deoxynojirimycin (**13**, marketed as Zavesca) in what has become known as substrate reduction therapy (SRT). Not clinical practice yet but an approach receiving considerable attention from academia and pharmaceutical industry alike is termed pharmacological chaperone therapy (PCT), which aims at stabilizing genetically impaired GBA1 to such an extent that (close to) normal glucosylceramide levels are reached. *N*-Nonyl-deoxynojirimycin (**12**) is a competitive GBA1 inhibitor that is under investigation as a pharmacological chaperone.[25] Its mode of action relies on its inhibitory activity: by active site occupation the enzyme 'folds' around the inhibitor and thus retains its active conformation. CMT has in fact reached the clinic for another LSD: Fabry disease (characterized by genetic deficiency in lysosomal alpha-galactosidase). *N*-Butyl-deoxygalactonojirimycin, or migalastat (**11**) is an α-galactosidase inhibitor and patients suffering from Fabry disease[26] can be treated with this compound, in combination with recombinant α-galactosidase (thus, a combined ERT/PCT treatment regime).

***Figure 3**: Structures of migalastat, NN-DNJ and Zavesca*



11, migalastat **12**, NN-DNJ **13**, Zavesca

The anti-viral activity of iminosugars is generally thought to be related to their ability to inhibit endoplasmic reticulum (ER) α-glucosidases. Blocking ER α-glucosidases affects the folding and trafficking of viral envelops glycoproteins.[27] Potent α-glucosidase inhibitors such

as DNJ (**1**), NN-DNJ (**12**) and castanospermine (**5**) have been subjected to clinical studies in relation to HIV infections, though no clinical drug has emerged from these studies.

In a recent publication, the anti-influenza activity of iminosugars was reported. In assays on infected cells both NN-DNJ and NB-DNJ were found to display antiviral activity against human influenza A, with NN-DNJ being the more potent compound. This activity is also thought to be related to ER α-glucosidase inhibition, since, upon treatment with **12** levels of viral hemagglutinin and neuraminidase proteins were found to be reduced.[28] Related studies have shown that iminosugars may block intracellular proliferation of yet another pathogenic virus: hepatitis B virus (HBV).

Outline of the thesis:

The research executed in the context of this Thesis comprises the design and synthesis of focused libraries of unprecedented iminosugars. **Chapter 2** reviews one of the most effective routes of synthesis towards deoxynojirimycin derivatives that is also central to parts of this Thesis: double reductive amination on an appropriately functionalized 5-keto-aldehyde. Application of this strategy in the synthesis of glycosylated DNJ derivatives is presented in **Chapter 3**. In **Chapter 4**, a series of *N*-alkyl iminosugars was designed and synthesized as selective inhibitors of the neutral glucosylceramidase, GBA2. In **Chapter 5**, and based on the dual GCS/GBA2 inhibitor described in the literature, biphenyl-L-*ido*-DNJ, a series of modified biphenyl-L-*ido* DNJ iminosugars are designed and synthesized and evaluated on their activity and selectivity on the three glucosylceramide processing enzymes, GCS, GBA1 and GBA2. In **Chapter 6**, a focused library of iminosugars characterized by the presence of a geminal bis(hydroxymethyl) motif is described, and **Chapter 7** summarizes the results described in this Thesis, presents plans for future research and details some initial steps that have been taken in this direction.

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2 Synthesis of Deoxynojirimycin and its Substituted Analogues: Highlights from the Literature

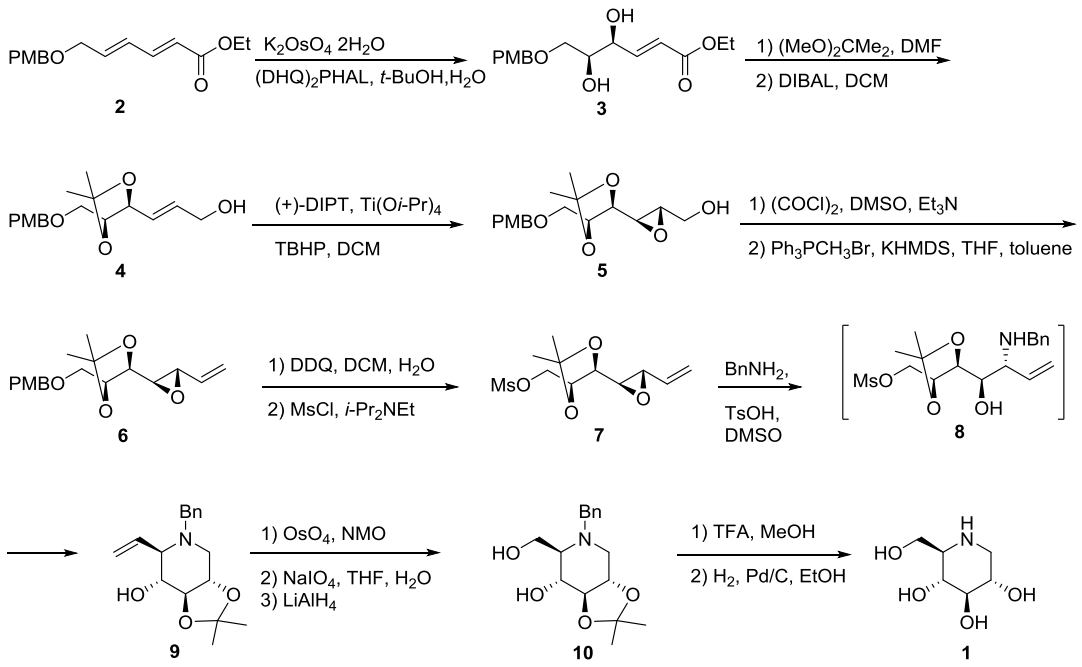
Introduction

Following the first synthesis of nojirimycin (NJ) and deoxynojirimycin (DNJ) reported by Paulsen and co-workers in 1967,[1] many studies on the synthesis of iminosugar derivatives have emerged.[2-7] In the course of these studies, many conceptually different strategies have been developed. Most of these synthesis strategies can be classified as being part of two overarching strategies, namely, those starting from simple, often achiral starting materials (*de novo* synthesis) and those starting from an abundant natural compound (chiral pool synthesis). Perhaps not surprisingly, carbohydrates often feature as the chiral pool starting material: many monosaccharides are abundant in nature, and a wealth of chemical transformations is known

by means of which the individual functional groups of a carbohydrate can be addressed individually. Last but not least, many of these functional groups present in the target iminosugar are also found in the parent sugar and therefore 'just' need to be retained in a synthesis campaign. In this chapter, a literature survey of some of the most versatile *de novo* synthesis and chiral pool-based synthesis strategies towards the archetypal iminosugar, 1-deoxynojirimycin (DNJ) will be given, with a focus on reductive amination chemistry as a key step in the synthesis.

Synthesis from achiral compounds

***Scheme 1**: Synthesis of DNJ featuring consecutive Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation steps*



The synthesis of DNJ, which has four consecutive chiral centers, from non-chiral starting materials can be time-consuming and requires both the introduction (through for instance the use of chiral auxiliaries or the application of asymmetric catalysis strategies) and the transfer of chirality.[5, 8-13] One of the earliest examples of an asymmetric synthesis of DNJ was reported by Somfai and co-workers in 1998 (Scheme 1).[14] In the first step of this synthesis *p*-methyloxybenzyl (PMB) protected diene **2** was subjected to a Sharpless asymmetric dihydroxylation reaction (treatment with AD-α-mix), giving diol **3** in high enantiomeric excess. Protection of the secondary alcohols in **3** was followed by reduction of the ethyl ester to

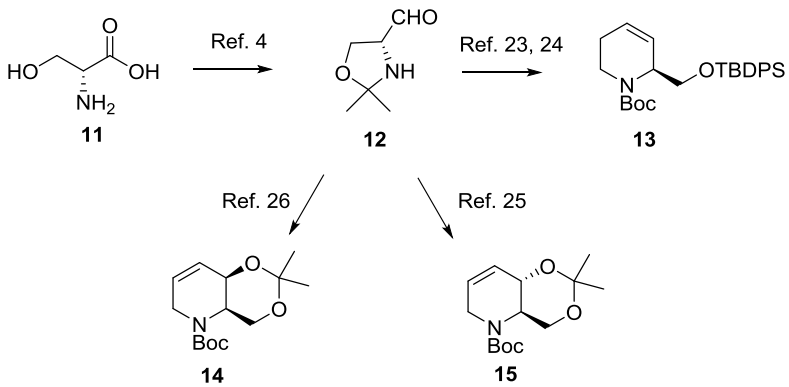
generate allylic alcohol **4**, which was converted to epoxide **5** by means of a Sharpless asymmetric epoxidation. Swern oxidation of the primary alcohol **5** to the aldehyde was followed by Wittig olefination, yielding vinyl epoxide **6** as a key intermediate bearing four consecutive chiral carbon centers.

Oxidative removal of the PMB group in **6** was followed by reaction of the thus liberated primary alcohol with methanesulfonyl chloride and diisopropylethyl amine to provide mesylate **7**. Treatment of **7** with benzylamine gave regioselective opening of the epoxide to *in situ* form compound **8**, after which intramolecular substitution of the mesylate in **8** provided piperidine **9**. Dihydroxylation of the vinyl moiety in **9** followed by oxidative cleavage and reduction of the resulting aldehyde gave partially protected DNJ **10** and ensuing global deprotection finally yielded DNJ **1**.

Synthesis from amino acids

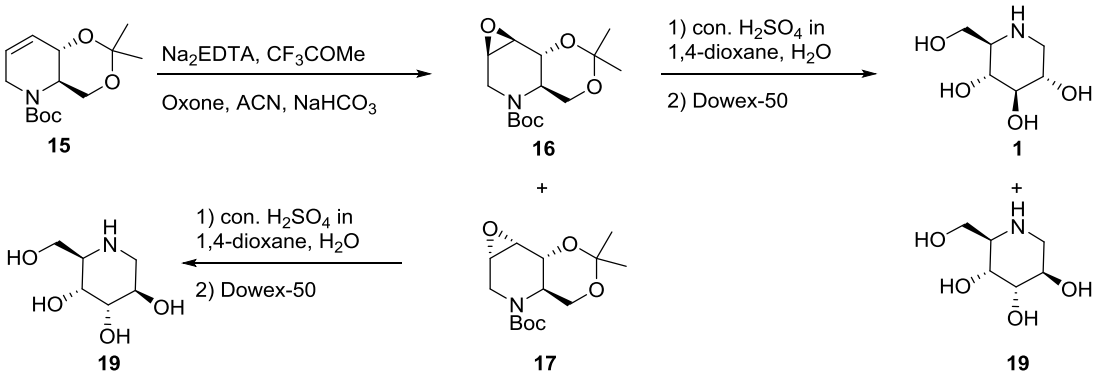
Compared with *de novo* synthesis strategies relying on the introduction of chirality during chemical transformations and that start with achiral starting materials, routes starting with chiral pool compounds are often more concise. Amino acids are sometimes used as starting points in the synthesis of iminosugars, and several routes of synthesis starting from (*S*)-isoserine,[15] serine[16-21] and alanine[22] have been reported. A relevant example of such a strategy is depicted in Scheme 2 and comprises the use of Garner's aldehyde **12**, itself easily prepared from D-serine, in the preparation of a variety of protected and functionalized piperideines.[4] These chiral piperideines (**13** - **15**) function as advanced intermediates in the preparation of DNJ (**1**) and some configurational analogues. D-Fagomine and its isomers were generated from methoxypiperideine **13**,[23, 24] DNJ and its D-*allo*, D-*altro* and D-*manno* congeners are synthesized via the dioxanyl piperideine intermediate **15**,[25] while D-*gal*, D-*gulo*, D-*ido* and D-*talo* isomers are generated from **14**.[26]

Scheme 2**: Chiral building blocks from Garner's aldehyde **12



As an example of how piperideines can serve as advanced intermediates towards iminosugars, the transformation of **15** to DNJ **1** is depicted in Scheme 3. Treatment of **15** with oxone gave a near equimolar amount of the two epoxides **16** and **17** (44% and 45% yield, respectively). Acid hydrolysis of **16** gave a mixture of DNJ (**1**) and its D-*altro* epimer (**19**), again in a 1:1 ratio. Under the same conditions **17** was transformed to the D-altro epimer as the sole product.

Scheme 3**: Synthesis of DNJ from piperideine **15



Takahata and co-workers revealed the use of the D-serine-derived piperideines in the synthesis of both configurational DNJ isomers and configurational fagomine isomers resembling naturally occurring D-configured monosaccharides. Moreover, by switching to the Garner's aldehyde derived from L-serine the corresponding enantiomeric isomers can be prepared following the same sequence of reactions. A recent route reported by Singh *et al*. describes such a synthesis of L-DNJ starting from L-serine-derived Garner's aldehyde.[21,27]

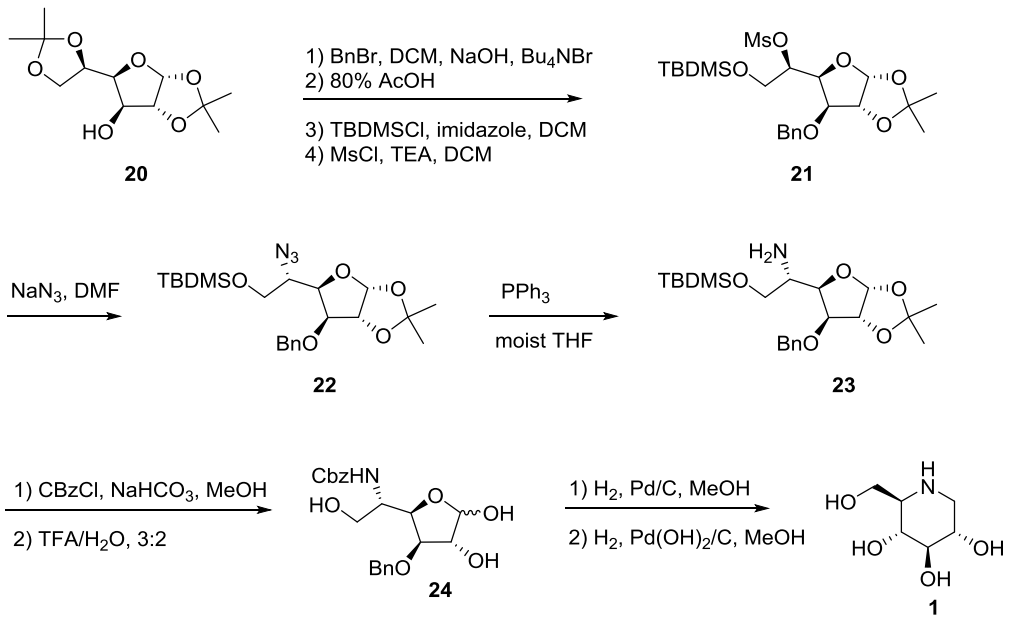
Synthesis from carbohydrates

Carbohydrates are often used as starting point for the chemical synthesis of iminosugar derivatives. Mannitol,[28, 29] D-ribose,[30] D-fructose[31] as well as a number of other monosaccharides all feature in iminosugar synthesis strategies, and a reductive amination event (single or double) often is applied to create the piperidine core structure.[32-48]

Owing to the structural similarity of DNJ and glucose, the use of glucose and its derivatives as chiral pool starting compounds is obvious, and many groups have devoted efforts to the synthesis of DNJ using glucose as starting material. One popular approach that starts from D-glucose is to prepare DNJ via a 5-azido intermediate.[32-40] A representative example is given in Scheme 4.[39] The synthesis scheme starts with diacetone glucose, and after a series of standard protective group and functional group transformations compound **21** featuring a mesylate at C-5 is obtained. S_N2 substitution of the mesylate by sodium azide yielded **22**, after which

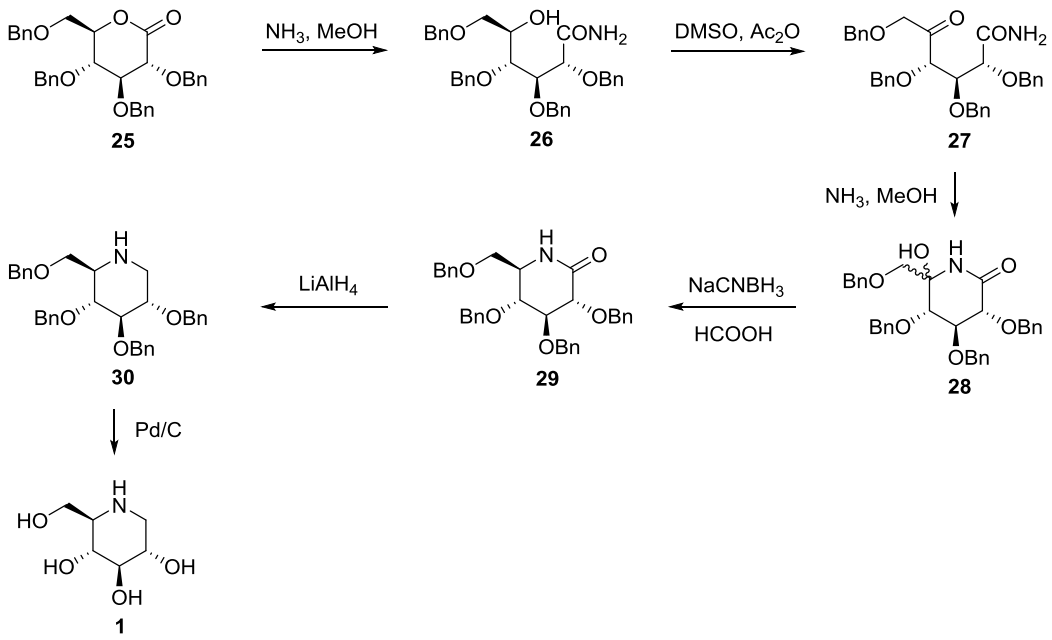
Staudinger reduction (**22** to **23**), Cbz protection of the amine in **23** followed by acidolysis provided lactol **24**. Compound **24** was subjected to catalytic hydrogenation, resulting in deprotection of the amino group, intramolecular nucleophilic attack of the amine on the aldehyde (masked in **24** as the hemi-acetal) and dehydration to *in situ* form the imine, which is reduced in one pot to form DNJ (**1**). The last steps – imine formation followed by reduction, in other words a reductive amination, is found in many DNJ synthesis schemes.

***Scheme 4**: Synthesis of DNJ via C-5 azido intermediate*



Two closely related DNJ syntheses that start from perbenzylated D-gluconolactone was reported independently by two groups about 25 years ago.[41-43] In a representative procedure (see in Scheme 5), 2,3,4,6-tetra-*O*-benzyl-α-glucopyranose was oxidized to lactone **25**. Treatment of **25** with methanolic ammonia gave 5-hydroxylamide **26**. The C-5 hydroxyl group was then oxidized to the ketone (**27**), after which ring closure provided hydroxylactam **28**. Reduction of the hydroxylactam under acidic conditions (*in situ* formation of an *N*-acyliminium ion, which is then reduced thanks to the presence in the reaction mixture of sodium cyanoborohydride) provided lactam **29**. Lithium aluminum hydride reduction of the lactam to the piperidine followed by catalytic hydrogenation to remove the benzyl protective groups yielded DNJ (**1**) in 29% yield over the 7 steps starting from 2,3,4,6-tetra-*O*-benzyl-α-glucopyranose.

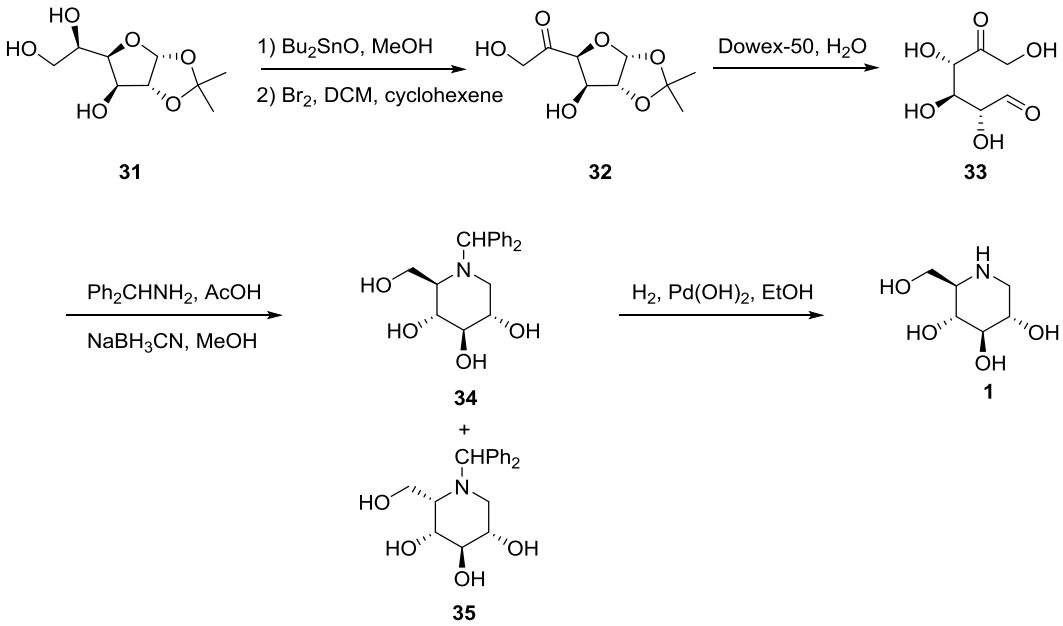
***Scheme 5**: Synthesis of DNJ from gluco-δ-lactone*



Synthesis via double reductive amination

Baxter and Reitz reported in 1990[44, 45] the first synthesis of DNJ featuring as key step a stereoselective intramolecular reductive amination of a 1,5-dicarbonyl derivative (**33**) (scheme 6). The synthesis of **33** started from acetone-D-glucose **31**. In the first step, the free secondary alcohol in **31** is oxidized with dibutyltin oxide and bromine, after which the isopropylidene group was removed with acid resin to give dicarbonyl compound **33**. This intermediate was subjected to a double reductive amination procedure using sodium cyanoborohydride and the appropriate primary amine to form *N*-substituted piperidines (**34** and **35**) with a high stereoselectivity (**34**:**35** = 96:4). The yield and stereoselectivity in the formation of the *N*-alkyl DNJ derivatives described in this report was found to depend on the primary amine used.[44] Application of the double reductive amination protocol to either peracetylated or perbenzylated **33** gave much lower yields.[45] Due to the high stereoselectivity and because hydroxyl protecting groups are not required, the double reductive amination procedure is very attractive and is widely applied in the preparation of different iminosugars and iminosugar derivatives.

***Scheme 6**: Double reductive amination procedure towards DNJ*

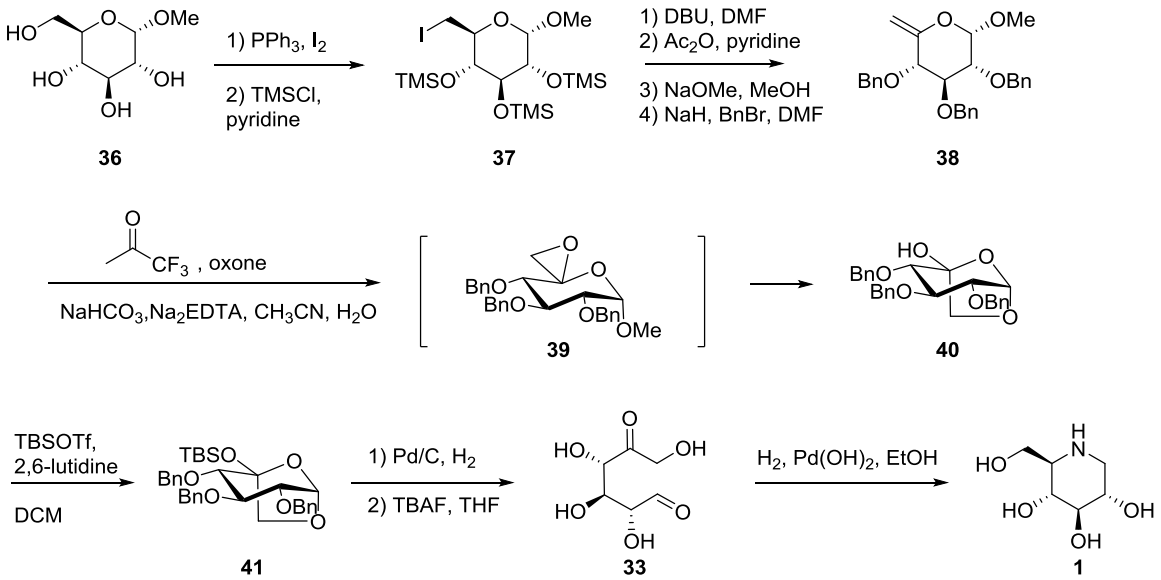


Different synthesis strategies have been developed to prepare hexos-5-uloses (**33**) for ensuing application in double reductive amination protocols.[46] For example, exo-glucal **38** can be transformed into 1,5-dicarbonyl **33** as depicted in scheme 7.[47] Compound **38** was generated from fully protected 6-deoxy-6-iodoglucopyranose **37**, which in turn was obtained in 2 steps from α-methyl glucose following treatment with DBU and ensuing protective group manipulations. Oxidation of **38** with 1,1,1-trifluoroacetone and oxone generated oxirane **39**, which was *in situ* hydrolyzed to give D-hexos-5-ulose **40**, after which subsequent silylation gave **41**. Removal of the protecting groups yielded 5-oxo-aldehyde **33**, which was converted into DNJ following conditions essentially as described by Baxter and Reitz.[45]

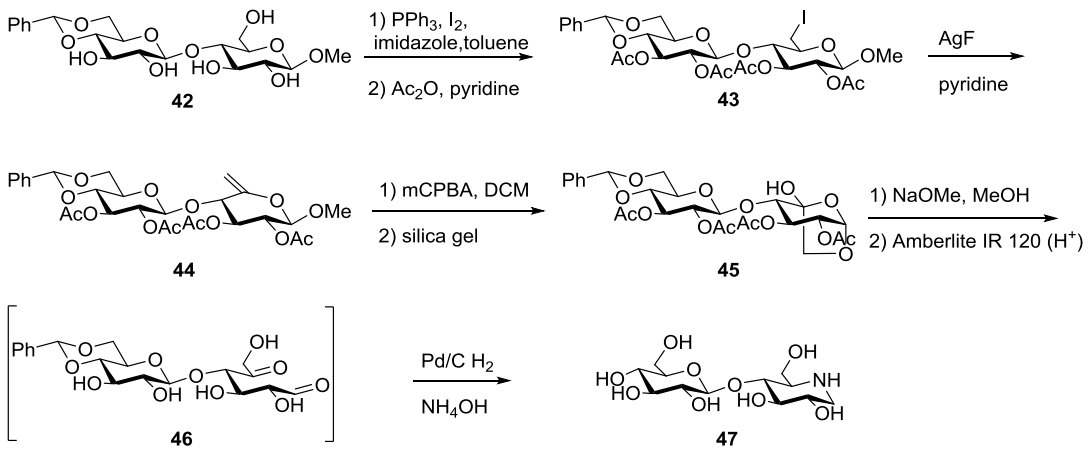
This strategy – generation of an exo-glucal and conversion to the keto-aldehyde – can be carried out on appropriately functionalized disaccharide derivatives as well. Steiner *et al*. developed a route to synthesize glucosyl-4-*β*-DNJ from cellobiose via a 5,6-glucal intermediate (Scheme 8).[48] In this synthesis, cellobiose was converted to its methyl cellobioside and the 4', 6' hydroxyl groups protected to give benzylidene acetal **42**. Following treatment with PPh_3 and iodine, the remaining free hydroxyl groups were acetylated to provide **43**. Silver fluoride mediated elimination of hydrogen iodide formed 5,6-enone **44**, the alkene moiety of which was epoxidized (treatment with mCPBA) after which *in situ* hydrolysis of the anomeric acetal formed **45**. Deacetylation (**45** to **46**) followed by double reductive amination yielded **47** (the

benzylidene protective group is removed under the applied conditions as well). This methodology can also be applied for the synthesis of glucosyl-4-α-DNJ from maltose.[48]

***Scheme 7**: Synthesis of DNJ via a 5,6-exo-glucal intermediate*



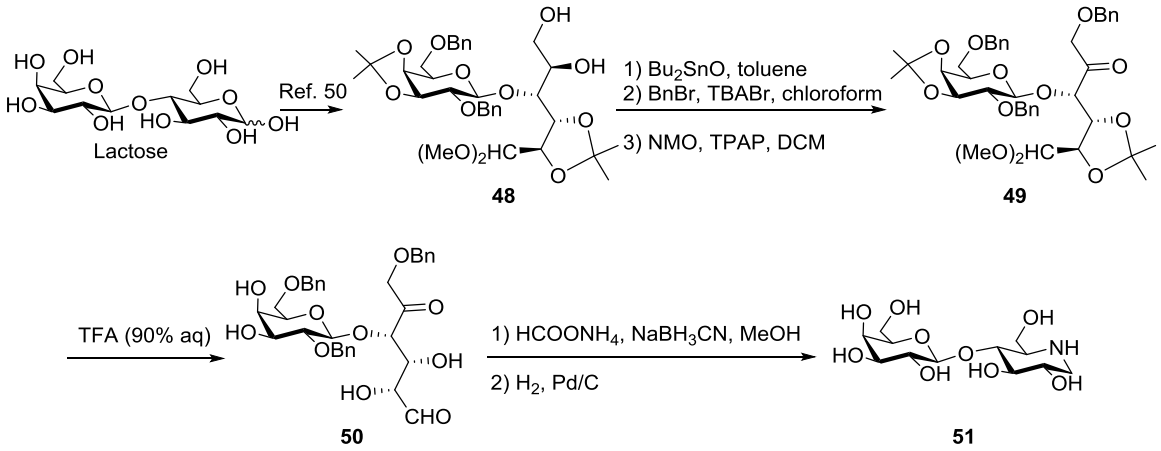
***Scheme 8**: Synthesis of gluco-4-β-DNJ via 5,6-intermediate intermediate*



A related 5-ulose compound proved also to be a versatile intermediate in the synthesis of galactyl-4-β-DNJ **51** as depicted in Scheme 9.[49] Lactose was transformed into partially protected disaccharide **48** in a series of standard transformations,[50] after which 6-*O*-benzyl protected ketone **49** was obtained through regioselective benzylation and oxidation of the remaining secondary alcohol. Treatment of **49** with 90% aqueous TFA gave 1,5-di-carbonyl

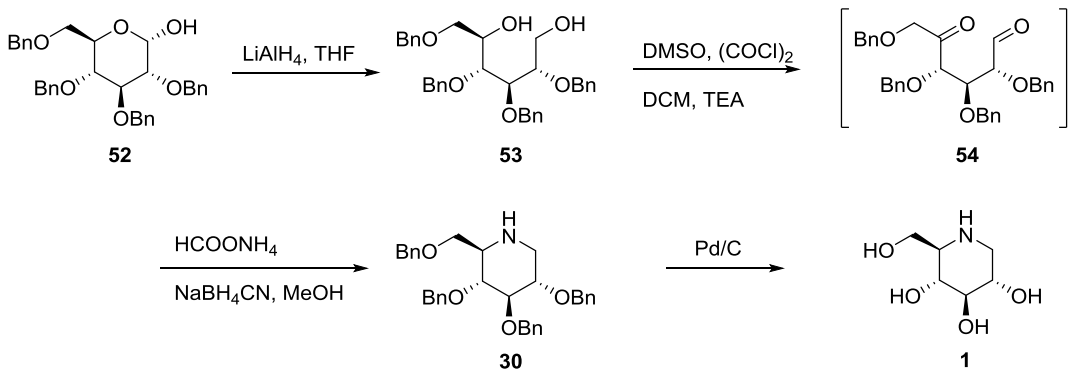
disaccharide **50**, which was subjected to double reductive amination. Finally, catalytic hydrogenation of the thus obtained partially protected aza-disaccharide gave target iminosugar **51**.

*Scheme **9**: Synthesis of galacto-4-β-D-DNJ from lactose*



As a last example, returning to the synthesis of DNJ **1**, a concise synthetic route with perbenzylated 5-keto-aldehyde intermediate **54** as key intermediate is depicted in Scheme 10. The synthesis starts from commercially available 2,3,4,6-*tert*-*O*-benzyl-glucose (**52**).[51] Lactol **52** was reduced by lithium aluminum hydride to give 1,5-diol **53**. Swern oxidation of both primary and secondary alcohol in **53** and subsequent double reductive amination of crude **53** yielded 2,3,4,6-tetra-*O*-benzyl-DNJ **30**. Palladium-catalyzed hydrogenolysis of the benzyl ethers in **30** yielded DNJ. The overall yield in this procedure is up to 65% starting from **52** and moreover the procedure can be executed on a multi-gram scale.[52]

Scheme 10**: Synthesis of DNJ from 2,3,4,6-tert-O-benzyl-glucose **52** via 1,5-diol intermediate **53



Summary

This chapter details some representative and versatile routes of synthesis to obtain DNJ **1** and some structural and configurational analogues. Amongst the routes presented, those starting from carbohydrates, and in particular those featuring double reductive amination steps, are arguably the most versatile for the construction of DNJ type iminosugars. Such routes proceed through the synthesis of a 5-keto-aldehyde intermediate, and thus the stereocenter at C-5 is lost during the synthesis. This stereocenter however is in almost all examples presented close to completely recovered during reduction of the intermediate imine. Thus the strategy is particularly suited for the construction of DNJ-configured iminosugars, although it should be noted that the synthesis of differently configured iminosugars by means of a double reductive amination step is likely to be less effective.

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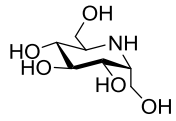
3 Synthesis of Glycosylated 1-Deoxynojirimycin

Introduction

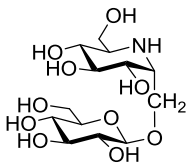
Iminosugars have received considerable interest in the past decades because of their potential to inhibit glycosidases and glycosyl transferases. A relatively unexplored class of iminosugars comprises the glycosylated deoxynojirimycin derivatives. Whereas monosaccharide analogues act as exoglycosidase inhibitors and sometimes also as glycosyl transferase inhibitors, iminosugars functionalized with a monosaccharide or an oligosaccharide may well act as inhibitors of another major class of glycoprocessing enzymes: endoglycosidases.

The glycosylated iminosugar, MDL25637 (**2**), is a relevant example of the potential of this class of compounds. It is a potent trehalase inhibitor (which is an established target for the treatment of type 2 diabetes), in contrast to the corresponding monosaccharide iminosugar, α-homonojirimycin (**1**), which does not inhibit this endoglycosidase activity.[1]

***Figure 1**: Structure of α-homonojirimycin and MDL25637*



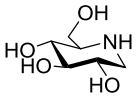
1, α-homonojirimycin



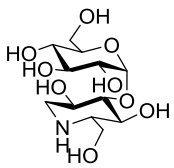
2, MDL25637

Glycosylated iminosugars have been isolated from plants and microorganisms, often organisms that also produce DNJ. However, their natural abundance is usually rather low. For instance, in order to isolate 50 mg of α-glucosylated deoxynojirimycin **4** (Figure 2), 50 kg of mulberry tree root bark is required.[2] The synthesis of glycosylated DNJ derivatives is therefore an attractive alternative. Three conceptual approaches can be discerned by means of which glycosylated DNJ have been prepared. These are 1) enzymatic glycosylation of DNJ derivatives, 2) chemical glycosylation of DNJ derivatives and 3) strategies based on disaccharide entities as starting material.

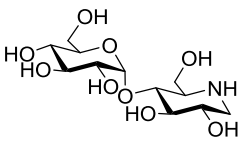
***Figure 2**: Structure of DNJ and glucosylated DNJ derivatives*



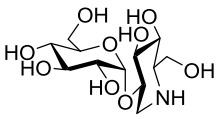
3, DNJ



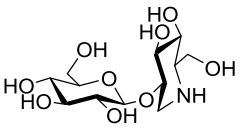
4



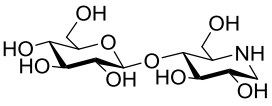
5, *malto*-DNJ



6



7

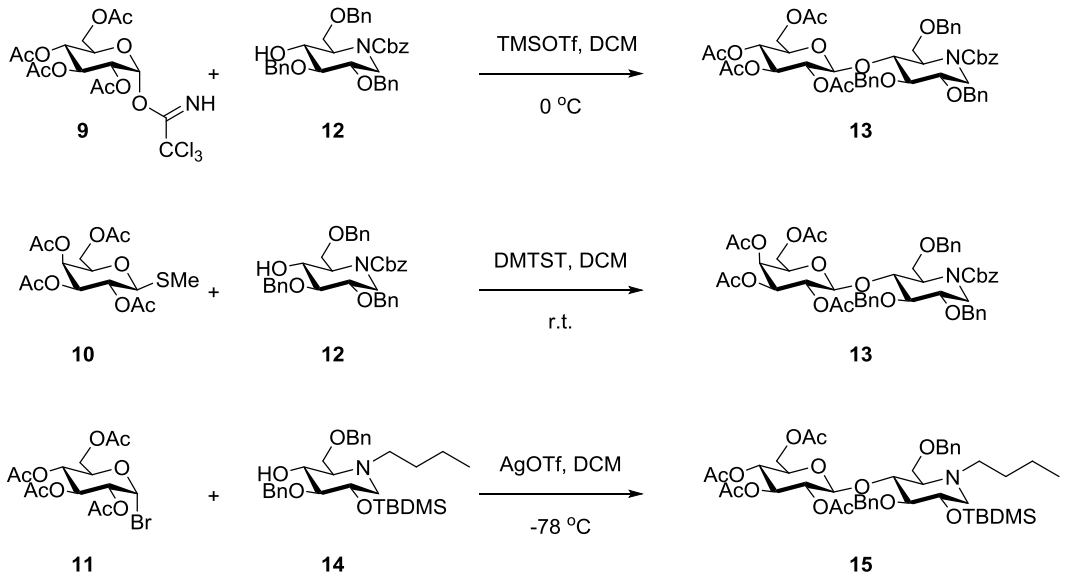


8, *cellobio*-DNJ

The enzymatic glycosylation of DNJ derivatives has been accomplished using glycohydrolases as catalysts in transglycosylation events using an appropriate donor glycoside. One of the earliest endeavors in this vein comprises the synthesis of compound **5** (Figure 2)

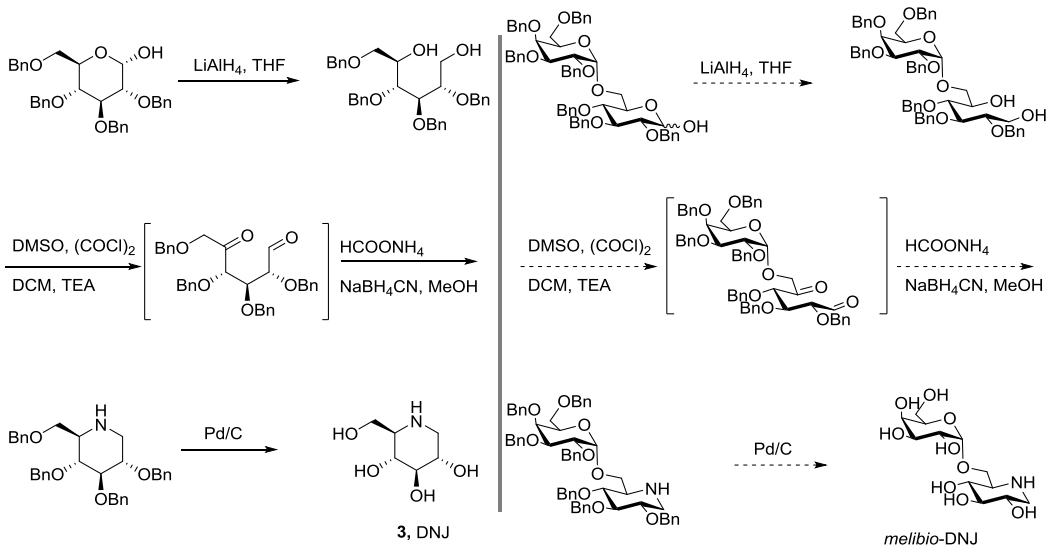
using α-cyclodextrin as glucose donor and *bacillus macerans* amylase as transglycosylase.[3] Following these studies, it was shown that a variety of alternative glycosides including *p*-nitrophenyl-α-D-galactose,[4] UDP-glucose,[5] and lactose[6] are effective donor glycosides as well, expanding the methodology to yield a variety of glycosylated DNJ derivatives. Besides glycosidases also glycosyl transferases have been recruited in the enzymatic synthesis of glycosylated DNJ derivatives. Enzymatic approaches hold several advantages, including mild reaction conditions, readily available starting material and short reaction sequences. However, enzymatic synthesis also has its limitations, including structural diversity that can be obtained in general and, in particular in the use of transglycosylations, the potential formation of structural isomers. For example, when cellobiose was chosen as glycosyl donor and yeast β-glucosidase as the transglycosylase catalyst, **4**, **6**, **7** and **8** (Figure 2) as well as a number of other oligosaccharides were formed as a mixture.[7] Because of their similar chemical and physical properties, separation of such a mixture of glycosylated iminosugars can be a challenge.

***Scheme 1**: Examples of chemical glycosylations of DNJ*



Chemical glycosylation forms an attractive alternative for enzymatic glycosylation of DNJ. In chemical glycosylation approaches, part of the hydroxyl groups in the acceptor (in this case, DNJ) are selectively protected, leaving the hydroxyl to be modified free for glycosylation using an appropriate donor (1-trichloroacetimidate **9,**[8] 1-thioglycoside **10**[9] or 1-bromoglycoside **11,**[10] scheme 1) and activation strategy. Since the synthesis of a donor and acceptor may take quite a few protection and deprotection steps, this strategy may be – compared to enzymatic synthesis - somewhat lengthy and tedious.

***Scheme 2**: Synthesis of DNJ[11] and proposed synthesis of melibio-DNJ via double reductive amination.*



The third conceptual strategy towards glycosylated DNJ derivatives that has been studied to some extent comprises the use of disaccharides as starting material. In this strategy multistep preparation of the donor and acceptor moieties is avoided, but the caveat is that appropriate disaccharide starting materials should be available. The transformation of disaccharides into glycosylated DNJ derivatives described in this chapter is rooted in the double reductive amination strategy (Scheme 2, *melibio*-DNJ as example) by means of which a partially protected glucitol, in which the C-1 and C-5 alcohols are free for modification, can be transformed into DNJ (see for details on this strategy also Chapter 2). In this strategy, the anomeric center of a partially protected disaccharide is selectively exposed, and the hemi-acetal reduced to generate the key 1,5-diol intermediate. This diol is oxidized to the keto-aldehyde, which in a double reductive amination event to produce the target glycosylated DNJ derivative. An important feature of this scheme is the recovery of the stereocenter at C-5 of the newly formed iminosugar, which works well when the glucopyranose configuration is the desired one.

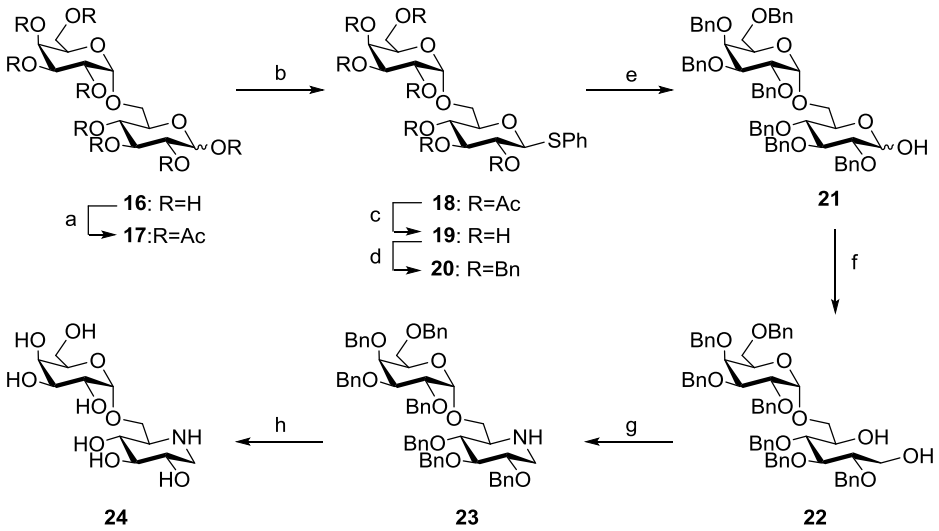
Results and discussion

Synthesis of 6-*O*-(α-D-galactopyranosyl)-1-deoxynojirimycin (24)

The synthesis of 6-*O*-(α-D-galactopyranosyl)-1-deoxynojirimycin **24** (*melibio*-DNJ) commences from melibiose **16**, which is commercially available. Treatment of **16** with sodium acetate in refluxing acetic anhydride afforded peracetylated melibiose **17**, which was reacted with thiophenol and $BF_3{\cdot}Et_2O$ to give thiophenyl melibioside **18**[12] in 74% yield over the two

steps. Zémplen deacetylation followed by benzylation yielded perbenzylated thiomelibiose **20**, the thiolphenyl group in which could be removed using literature conditions[13] (treatment with *N*-iodosuccinimide and trifluoroacetic acid) to yield lactol **21** as the key intermediate in 39% yield over the three steps.

***Scheme 3**: Syntheses of **24** from melibiose*

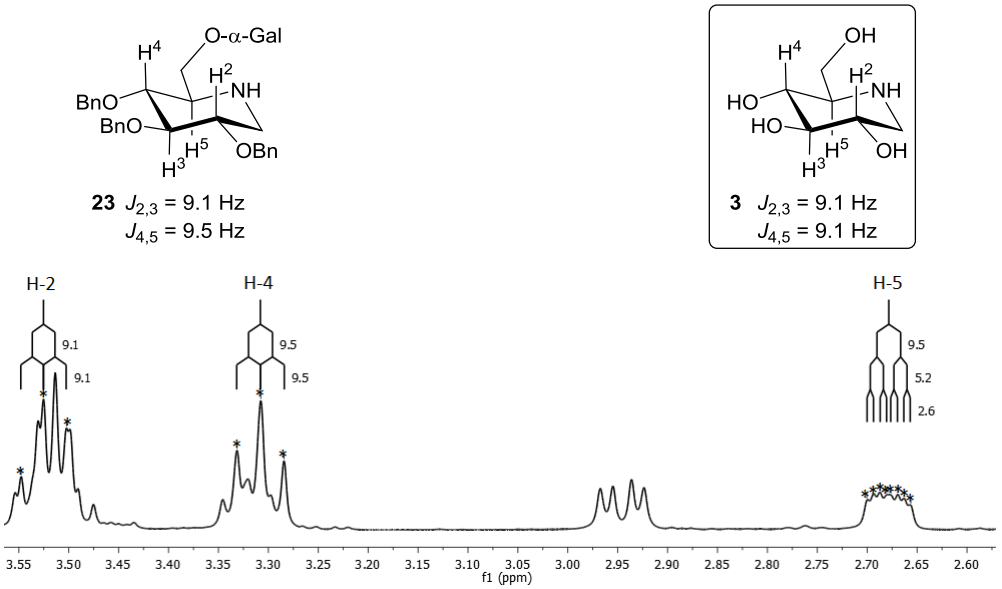


Reagents and conditions: [**a**] Ac_2O, NaOAc, reflux, 90%; [**b**] $BF_3{\cdot}Et_2O$, PhSH, DCM, 82%; [**c**] NaOMe, MeOH; [**d**] BnBr, NaH, DMF, 50% 2 steps; [**e**] NIS, TFA, DCM, 77%; [**f**] $LiAlH_4$, THF, 74%; [**g**] 1) $(COCl)_2$, DMSO; 2) $HCOONH_4$, Na_2SO_4, $NaBH_3CN$, 71% 2 steps; [**h**] 10% Pd/C, DMF/MeOH, 1M HCl, 75%.

In the next step, the hemiacetal moiety in **21** was reduced (lithium aluminum hydride) to give diol **22**, which was oxidized to the corresponding keto-aldehyde using Swern conditions. Double reductive amination with concomitant regeneration of the chiral center at C-5 was accomplished using ammonium formate and sodium cyanoborohydride to yield protected 1-*melibio*-deoxynojirimycin **23** (52% yield, three steps). The chirality of carbon C-5 in **23** was unambiguously established by proton NMR, revealing that, as expected, the iminosugar moiety in **23** has the D-*gluco*-configuration (as in DNJ). The coupling constants between H-4 and H-5 (9.5 Hz) and between H-2 and H-3 (9.1 Hz) are in full agreement with the presented stereochemistry of **23**, and the stereochemical outcome of the double reductive amination step is therefore as was observed previously for the synthesis of DNJ using the same sequence of events (reduction of the hemi-acetal in 2,3,4,6-tetra-*O*-benzyl-glucopyranose, followed by Swern oxidation of both primary and secondary alcohol and finally double reductive amination of the intermediate 5-keto-aldehyde, Figure 3, inserted box).[11] Removal of the benzyl groups in

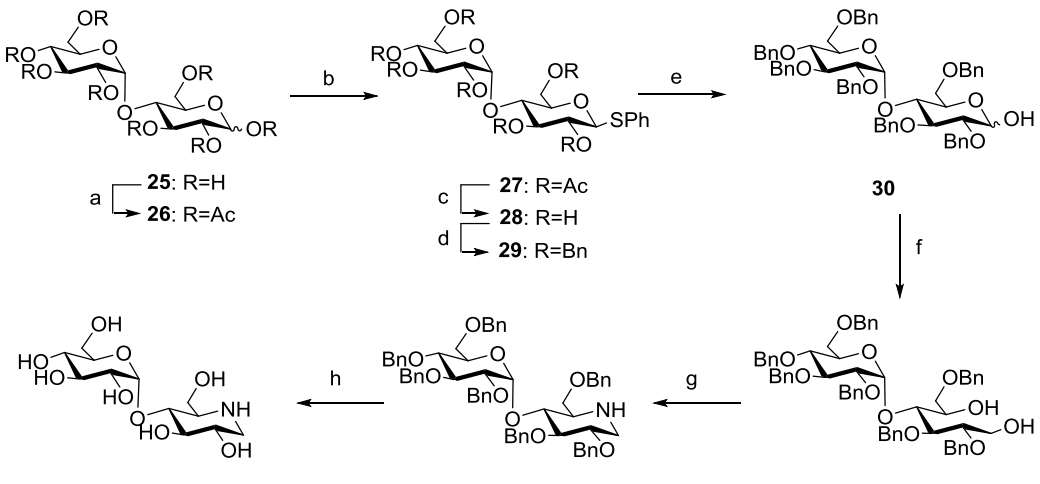
23 by palladium-catalyzed hydrogenation gave the target imino-disaccharide **24** in 11% overall yield starting from **16**.

Figure 3**: Part of the 400 MHz proton NMR spectra of **23



Synthesis of 4-*O*-(α-D-glucopyranosyl)-1-deoxynojirimycin (33)

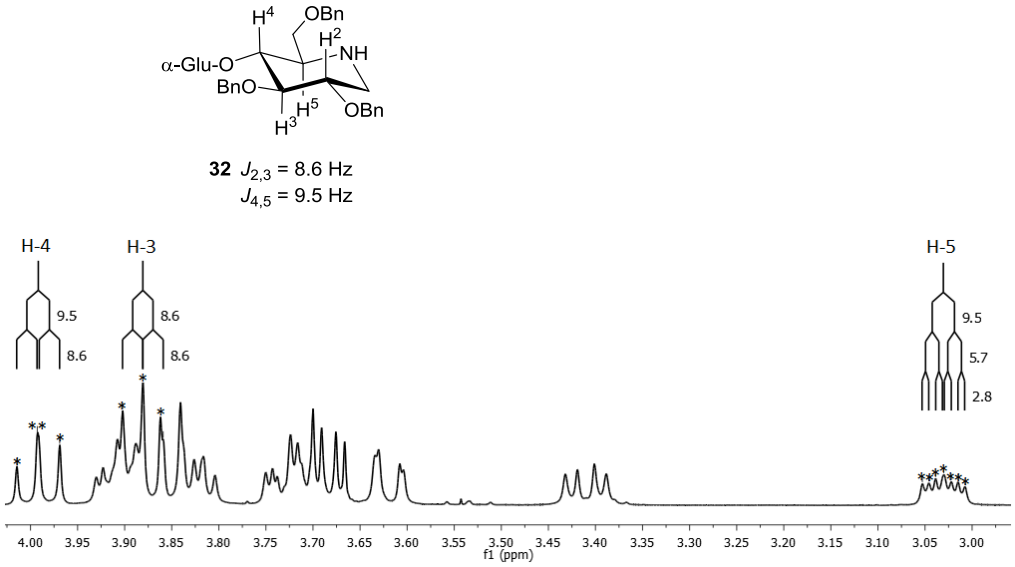
***Scheme 4**: Synthesis of **33** from maltose*



Reagents and conditions: [**a**] Ac_2O, NaOAc, reflux, 94%; [**b**] $BF_3{\cdot}Et_2O$, PhSH, DCM, 61%; [**c**] NaOMe, MeOH; [**d**] BnBr, NaH, DMF, 89%; [**e**] NIS, TFA, DCM, 93%; [**f**] $LiAlH_4$, THF, 74%; [**g**] 1) $(COCl)_2$, DMSO; 2) $CHOONH_4$, Na_2SO_4, $NaBH_3CN$, 44% 2 steps; [**h**] 10% Pd/C, DMF/MeOH, 1M HCl, 71%.

The synthesis strategy applied for the assembly of 4-*O*-(α-D-glucopyranosyl)-1-deoxynojirimycin **33** (*malto*-DNJ) was identical as that described for the synthesis of **24** (*melibio*-DNJ, scheme 3), but now starting from maltose (**25**). Lactol **30** was uneventfully obtained from maltose **25** in a yield of 47% over the five steps. Lithium aluminum hydride reduction of **30** followed by Swern oxidation and double reductive amination produced fully protected *malto*-DNJ **32** (33% yield, three steps). The stereochemical outcome in synthesizing **32** was revealed by proton NMR spectroscopy (Figure 4). The benzyl groups were removed by palladium-catalyzed hydrogenolysis to form target iminosugar **33** in 11% overall yield starting from (**25**).

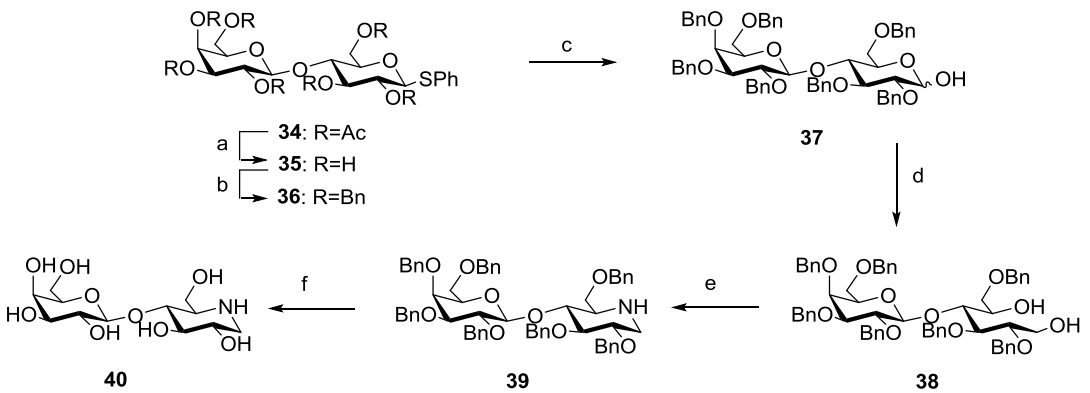
Figure 4**: Part of the 400 MHz proton NMR spectra of **32



Synthesis of 4-*O*-(β-D-galactopyranosyl)-1-deoxynojirimycin (34)

The synthesis of 4-*O*-(β-D-galactopyranosyl)-1-deoxynojirimycin **40** (*lacto*-DNJ) starts with lactose, which is one of the cheapest disaccharide known and is a side product of the dairy industry.[14] Hepta-acetyl thiolactoside **34** was prepared following the sequence of events as described for hepta-acetyl thiomelibioside **18**, but starting from lactose. Compound **34** underwent deacetylation, benzyl protection and NIS/TFA thioglycoside hydrolysis as described before to obtain lactol **37**, and was reduced (lithium aluminum hydride), subjected to Swern oxidation followed by double reductive amination to obtain protected imino-disaccharide **39**. Compound **39** was treated with palladium on carbon and hydrogen gas to give the desired imino-disaccharide **40** in 14% overall yield starting from **34**.

Scheme 5**: Synthesis of **34



Reagents and conditions: [**a**] NaOMe, MeOH; [**b**] BnBr, NaH, DMF, 100% 2 steps; [**c**] NIS, TFA, DCM, 85%; [**d**] $LiAlH_4$, THF, 77%; [**e**] 1) $(COCl)_2$, DMSO; 2) $HCOONH_4$, Na_2SO_4, $NaBH_3CN$, 22%; [**f**] Pd/C, H_2, DMF/MeOH, 64%.

The stereochemistry of carbon C-5 was established by NMR to be as in the parent compound. For comparison, the *J* values between H-2 and H-3 (not changed during the syntheses) and those of H-4 and H-5 (destroyed during Swern oxidation and recovered during reductive amination) of a number of aza-disaccharides discussed in this chapter is given in Table 1.

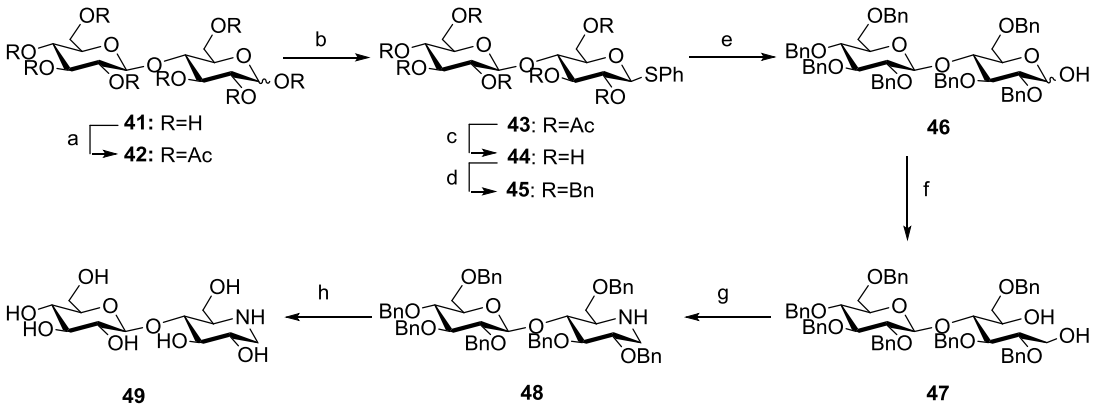
***Table 1:** $J_{2,3}$ and $J_{4,5}$ of DNJ moiety from different molecules*

Molecule	$J_{2,3}$ (Hz)	$J_{4,5}$ (Hz)
1-Deoxynojirimycin (DNJ), **3**	9.1	9.1
Protected *melibio*-DNJ, **23**	9.1	9.5
Protected *malto*-DNJ, **32**	8.6	9.5
Lacto-DNJ, **40**	8.6	9.5
Protected *cellobio*-DNJ, **48**	8.8	9.7
Protected 2-*O*-(α-gal)-DNJ, **68**	9.2	9.3

Synthesis of 4-*O*-(β-D-glucopyranosyl)-1-deoxynojirimycin (49)

Starting from disaccharide cellobiose (**41**), 4-*O*-(β-D-glucopyranosyl)-1-deoxynojirimycin **49** (*cellobio*-DNJ) was obtained in 10% overall yield following the sequence of events as described for the synthesis of **24** (*melobio*-DNJ). The nature of the stereochemistry at C-5 of the thus produced DNJ moiety in **48** was confirmed by NMR spectroscopy (table 1).

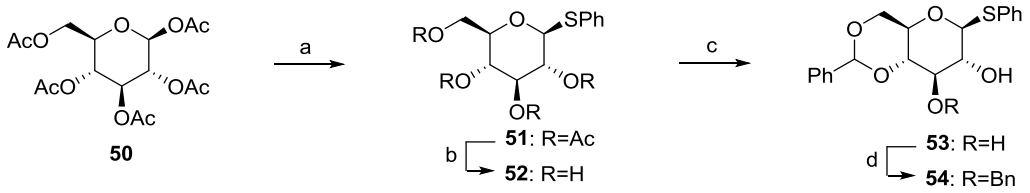
***Scheme 6**: Synthesis of **49** from cellobiose*



Reagents and conditions: [**a**] Ac_2O, NaOAc, reflux, 98%; [**b**] $BF_3{\cdot}Et_2O$, PhSH, DCM, 91%; [**c**] NaOMe, MeOH; [**d**] BnBr, NaH, DMF, 89%; [**e**] NIS, TFA, DCM, 90%; [**f**] $LiAlH_4$, THF, 74%; [**g**] 1) $(COCl)_2$, DMSO; 2) $HCOONH_4$, Na_2SO_4, $NaBH_3CN$, 44% 2 steps; [**h**] 10% Pd/C, DMF/MeOH, 1M HCl, 65%.

Synthesis of 2-*O*-(α-galactopyranosyl)-1-deoxynojirimycin (69)

Scheme 7**: Synthesis of acceptor **54



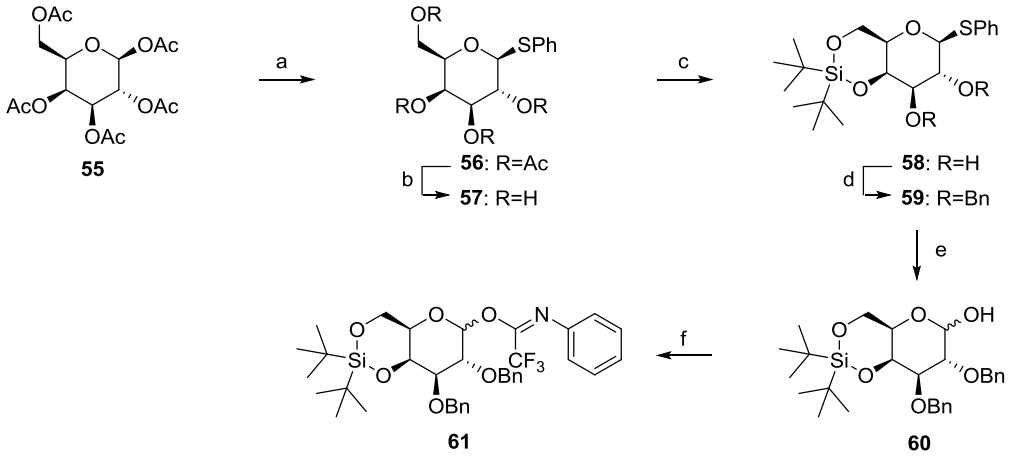
Reagents and conditions: [**a**] $BF_3{\cdot}Et_2O$, PhSH, DCM, 91%; [**b**] NaOMe, MeOH; [**c**] $PhCH(OMe)_2$, *p*-TsOH, DMF, 59% 2 steps; [**d**] Bu_2SnO, TBAI, BnBr, 73%.

The examples described above comprise the use of cheap, readily available disaccharides featuring a glucopyranose moiety at the reducing end as starting material. Obviously, many other disaccharides other than the ones used can be envisaged as starting material and that have a similar lay-out: a glycosylated glucopyranose. Besides making use of available disaccharides of this nature, one can also synthesize these by chemical glycosylation of a partially protected glucopyranose moiety. As an example, partially protected 1-phenylthio-glucopyranoside **54**, with O-2 free for chemical glycosyation, can be prepared following a number of protective group manipulations starting from peracetylated glucopyranose **50** (scheme 7).

Treatment of **50** with borontrifluoride diethyl etherate and thiophenol yielded thiophenylglycoside **51**, the acetyl groups in which were then removed using sodium methoxide to give **52**. The C-4 and C-6 hydroxyls in **52** were protected as the benzylidene acetal, after which regioselective benzylation (dibutyltin oxide, tetrabutylammonion iodide, benzyl bromide) gave **54** in 44% yield over the five steps.

Galactose donor **61** was selected as glycosylating species to functionalize O-2 in **54** prior to its transformation into a DNJ derivative. The synthesis of **61** starts from D-galactose and was accomplished in 7 steps. In the first step, all hydroxyl groups in D-galactose were transformed into the acetates using acetic anhydride and sodium acetate, yielding peracetylated galactopyranose **55**. Treatment of **55** with thiophenol and Lewis acid yielded **56**, which after treatment with sodium methoxide gave thiogalactoside **57**. The C-4 and C-6 hydroxyls in **57** were protected as the di-*tert*-butylsilylene acetal, to yield **58**. The free hydroxyls in **58** were protected as the benzyl ethers (treatment with benzyl bromide and sodium hydride) giving **59**. The thio-acetal linkage in **59** was cleaved (NIS/TFA, **59** to **60**), after which treatment with trifluoro-phenylacetimidoyl chloride gave donor galactoside **61** in an overall yield of 16% starting from galactose.

Scheme 8**: Synthesis of donor **61

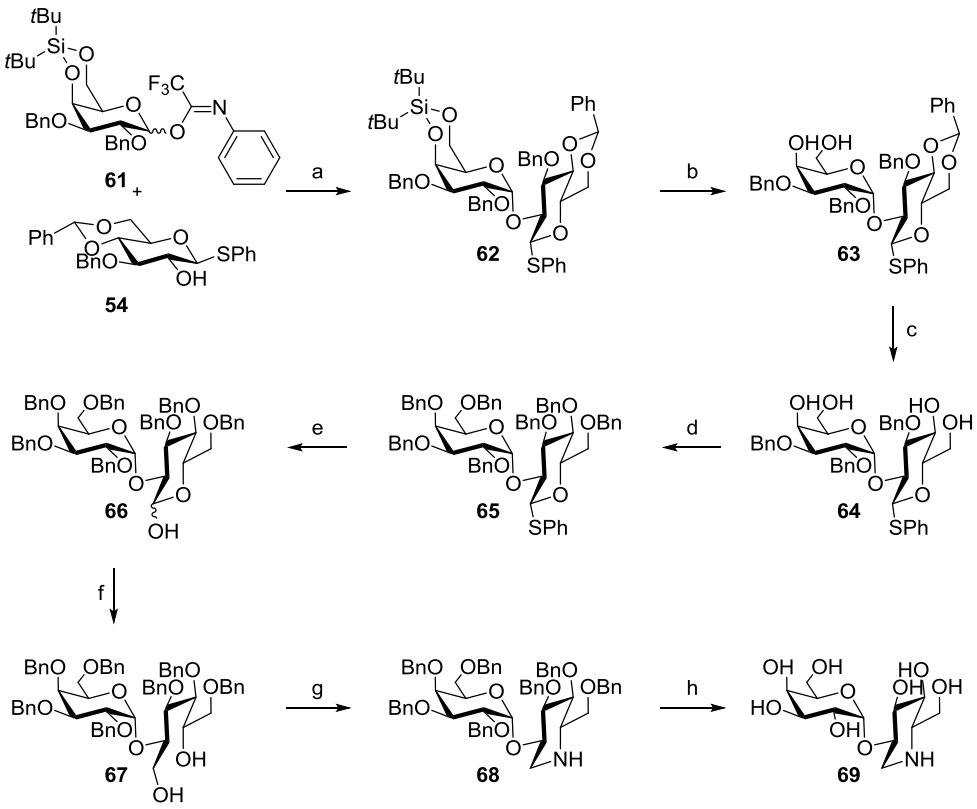


Reagents and conditions: [**a**] $BF_3{\cdot}Et_2O$, PhSH, DCM, 100%; [**b**] NaOMe, MeOH; [**c**] *t*BuSi(OTf)$_2$, 53% 2 steps; [**d**] BnBr, NaH, DMF, 56%; [**e**] NIS, TFA, DCM, 88%; [**f**] trifluoro-phenylacetimidoyl chloride, Cs_2CO_3, acetone, 65%.

Glucose acceptor **54** was next coupled with donor galactoside **61** using trimethylsilyl trifluoromethanesulfonate as the activating agent at 0 °C. Following this methodology, compound **62** was obtained as the main product in good stereoselectivity ($J_{1',2'}$ = 4.0 Hz) in a

yield of 69%. However, when the glycosylation was carried out at -78 °C, the main product proved to be thiophenyl galactopyranoside **59** (yield more than 70%), with no formation of the desired disaccharide **62** observed. When conducting this reaction at -20 °C, **62** was obtained in a yield of 35%, together with a considerable amount of **59** (30%).

Scheme 9**: Synthesis of **69

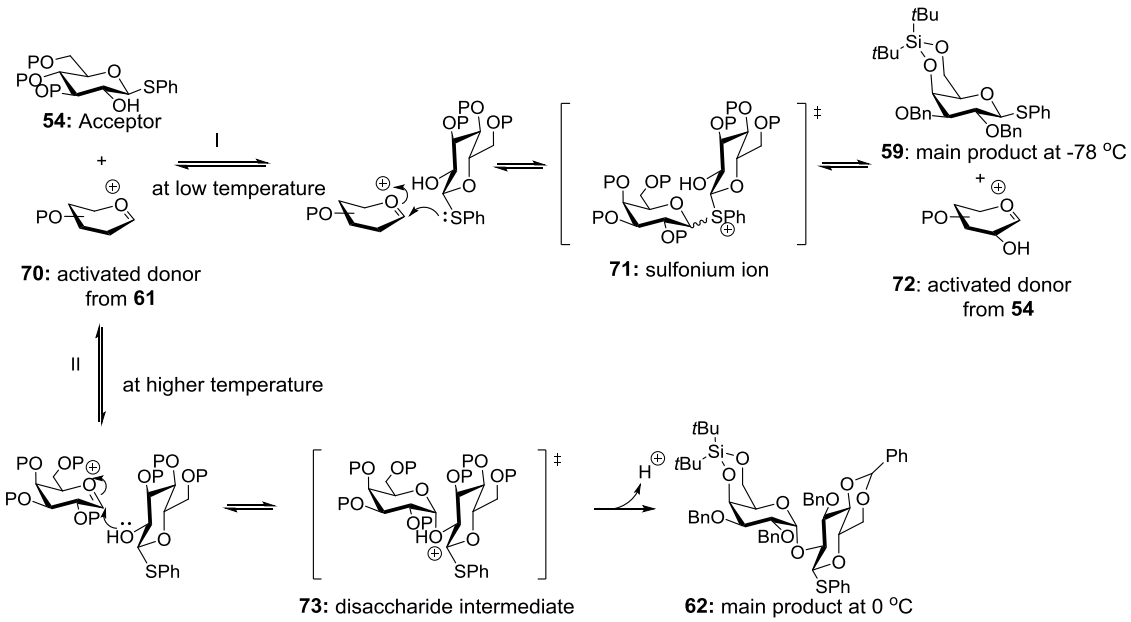


Reagents and conditions: [**a**] TMSOTf, DCM, 0 °C, 69%; [**b**] TBAF, THF, 82%; [**c**] *p*-TsOH, DCM, 90%; [**d**] BnBr, NaH, DMF, 92%; [**e**] NIS, TFA, DCM, 71%; [**f**] $LiAlH_4$, THF, 88%; [**f**] $(COCl)_2$, DMSO, $HCOONH_4$, Na_2SO_4, $NaBH_3CN$, 24%; [g] Pd/C, H_2, EtOH, 1M HCl, 52%.

The generation of **59** at low temperature might be due to the side reaction mechanism visualised in Figure 6. The sulfur and hydroxyl groups on the acceptor can both react with the activated donor, and whether the reaction goes through pathway I or pathway II depends on the relative reactivity of the sulfur and the hydroxyl groups.[15] There exists literature precedents reporting that lowering the temperature favors reaction pathway II and thus avoids the aglycon transfer product.[16-18] However, this is inconsistent with the findings presented here. Arguably, upon formation of oxycarbenium ion **70**, *S*-glycosylation (pathway I) to give sulfonium ion **71**

proceeds easier (thus at lower temperature) than *O*-glycosylation (pathway II) to give protonated disaccharide **73**. Once **73** is formed, however, deprotonation yields the final disaccharide as the thermodynamic end point. Assuming the occurrence of an equilibrium between sulfonium ion **71** and *in situ* formed oxycarbenium ion **70** (and acceptor **54**), and by allowing the formation of **73** as well (by elevating the temperature) the reaction will then proceed towards disaccharide **62**. In case the temperature is insufficiently high to overcome the barrier towards **73**, and therefore allowing only pathway I to occur, eventually expulsion of oxycarbenium ion **72** (which will deteriorate during work-up) may occur as the main conclusive event, delivering phenylthiogalactoside **59**.

***Figure 6**: Chemical glycosylation products at different temperatures*



With disaccharide **62** in hand, the corresponding aza-disaccharide was readily prepared using the sequence of events also used for the preparation of the other aza-disaccharides described in this chapter. In the first instance, the di-*tert*-butylsilylene ester in **62** was removed using tetra-*N*-butylammoniumfluoride (TBAF) to afford **63**. Removal (with *p*-toluenesulfonic acid) of the benzylidene in **63** gave **64** as white crystals (90%) and the free hydroxyls in **64** were benzylated (sodium hydride and benzyl bromide) to give **65**. NIS/TFA mediated hydrolysis of the phenyltio acetal yielded hemi-acetal **66**, which was subjected to $LiAlH_4$ mediated reduction to give diol **67** in a yield of 88%. Subsequent oxidation of both alcohols in **67** followed by the double reductive amination procedure gave protected iminosugar **68**.

Proton NMR spectroscopy of **68** confirmed that the DNJ configuration was obtained also in this instance (see table 1). The benzyl protecting groups in **68** were finally removed to give aza-disaccharide **69** in an overall yield of 7% based on **62**.

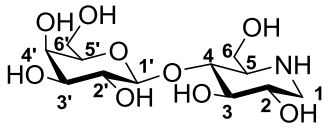
Conclusion

This Chapter reports on the synthesis of five glycosylated 1-deoxynojimycin derivatives. Four of these, namely 6-*O*-(α-D-galactopyranosyl)-1-deoxynojirimycin (**24**), 4-*O*-(α-D-glucopyranosyl)-1-deoxynojirimycin (**33**), 4-*O*-(β-D-glucopyranosyl)-1-deoxynojirimycin (**49**) and 4-*O*-(β-D-galactopyranosyl)-1-deoxynojirimycin (**40**) were synthesized from their commercially available disaccharide (melibiose, maltose, cellobiose and lactose, respectively) as precursor. As a further example, 2-*O*-(α-galactopyranosyl)-1-deoxynojirimycin (**69**) was also successfully synthesized via the same methodology from its corresponding disaccharide, and the precursor disaccharide for this transformation was synthesized via chemical glycosylation. Thus the methodology presented appears general and, though yields vary between the individual examples, glycosylated DNJ derivatives can be prepared without difficulties from their glycosylated glucose counterparts, as long as the latter are synthetically tractable.

Experimental Section

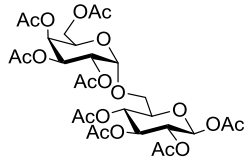
General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/ L) and K_2CO_3 (25 g/ L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography was performed on silica gel (40 - 63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz) or Bruker 600 (600/150 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[19] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150 - 2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ = 589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer provided by GE-Healthcare polymere HW-40S from Toyopearl, column size d = 26 mm; l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. Purification on HPLC were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 μm, 19 x 150 mm column).

***Figure 7**: Proton and carbon NMR numbering of iminosugars:*



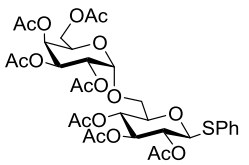
Synthesis of 6-*O*-(α-D-galactopyranosyl)-1-deoxynojirimycin (24)

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-β-glucopyranose (17):



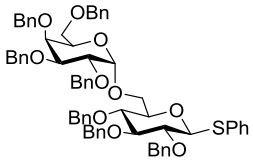
A suspension of Ac_2O (59.0 mL, 0.625 mol) and NaOAc (4.21 g, 51.3 mmol) were heated to reflux. When refluxing began the heat source was removed and melibiose (10.0 g, 29.2 mmol), which was co-evaporated with toluene (3 x), was added in small portions. The mixture was heated to reflux for 1 hour. TLC analysis confirmed complete consumption of the starting material **16** (1:1, PE:EtOAc, R_F = 0.39). The mixture was poured into ice water (400 mL) which was vigorously stirred. DCM (150 mL) was added and the layers were separated. The organic layer was washed with cold water (150 mL), sat. aq. $NaHCO_3$ solution (2 x 150 mL) and brine (150 mL). After the organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified with silica gel column chromatography (2:1 → 1:1 → 1:2, PE:EtOAc) to give **17** in 90% yield (17.8 g, 26.2 mmol). R_F = 0.39 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, *J* = 8.3 Hz, 1H, H-1), 5.45 (d, *J* = 2.9 Hz, 1H, H-4'), 5.34 (dd, *J* = 10.8, 3.3 Hz, 1H, H-3'), 5.27 (t, *J* = 9.4 Hz, 1H, H-4), 5.16 (m, 1H, H-1), 5.07 (m, 2H, H-2, H-3), 4.21 (dd, *J* = 11.4, 5.0 Hz, 1H, H-5'), 4.15 – 4.02 (m, 3H, H-2', H_2-6), 3.83 (ddd, *J* = 9.9, 3.9, 2.6 Hz, 1H, H-5), 3.74 (dd, *J* = 11.7, 4.3 Hz, 1H, H-6'a), 3.65 (dd, *J* = 11.8, 2.3 Hz, 1H, H-6'b), 2.24 – 1.96 (m, 24H, 8 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 – 169.1 (C=O), 96.5 (C-1'), 91.7 (C-1), 73.6 (C-5), 70.3 (C-3), 68.4 (C-4), 68.2 (C-4'), 68.1 (C-2), 67.6 (C-3'), 66.6 (C-5'), 65.8 (C-6), 61.9 (C-6'), 20.9 – 20.7 (8 x CH_3).

2,3,4-Tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-1-thio-D-glucopyranose (18):



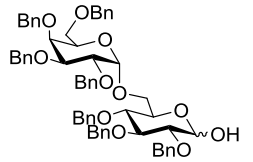
PhSH (5.2 mL, 51.0 mmol) was added to a stirred solution of **17** (17.8 g, 26.2 mmol) in dry DCM (50 mL) and kept under argon atmosphere. After cooling the solution (0 °C), $BF_3{\cdot}Et_2O$ (4.9 mL, 39.7 mmol) was added dropwise, turning the solution to orange. The mixture was stirred for 4 hours at r.t., after which TLC analysis showed complete consumption of the starting material. DCM (50 mL) was added to the reaction mixture and the solution was washed with sat. aq. $NaHCO_3$ solution (100 mL, 2 x). The organic layer was dried (Na_2SO_4). After filtering, concentrating and evaporating of the volatiles, the crude product was purified with silica gel column chromatography (3:1 → 7:3 → 5:3 → 1:1, PE:EtOAc), to give **18** as a pure white solid product in 82% yield (15.6 g, 21.4 mmol), R_F = 0.43 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.0, 1.4 Hz, 2H, H_{Ar} SPh), 7.40 – 7.30 (m, 3H, H_{Ar} SPh), 5.35 (dd, *J* = 3.5, 1.2 Hz, 1H, H-4'), 5.32 (dd, *J* = 10.2, 3.4 Hz, 1H, H-3'), 5.24 (t, *J* = 9.4 Hz, 1H, H-3), 5.14 (d, *J* = 3.7 Hz, 1H, H-1'), 5.11 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2'), 5.03 (t, *J* = 9.6 Hz, 1H, H-4), 4.96 (dd, *J* = 10.1, 9.2 Hz, 1H, H-2), 4.78 (d, *J* = 10.1 Hz, 1H, H-1), 4.21 (td, *J* = 6.6, 1.3 Hz, 1H, H-5'), 4.03 (d, *J* = 6.9 Hz, 2H, H_2-6'), 3.77 (dd, *J* = 10.6, 5.8 Hz, 1H, H-6b), 3.71 (dd, *J* = 5.8, 2.0 Hz, 1H, H-5), 3.56 (dd, *J* = 10.7, 1.9 Hz, 1H, H-6a), 2.15 – 1.99 (m, 21H, 7 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 – 169.4 (C=O), 132.2 (C_{Ar} Ph), 132.1 (C_q SPh), 129.3, 128.4 (C_{Ar} SPh), 96.4 (C-1'), 85.7 (C-1), 76.8 (C-5), 74.1 (C-3), 70.1 (C-2), 68.8 (C-4), 68.2 (C-2'), 68.2 (C-4'), 67.5 (C-3'), 66.9 (C-6), 66.6 (C-5'), 61.8 (C-6'), 21.0 – 20.7 (7 x CH_3). $[\alpha]^{20}_D$ = +73.3 (c = 1.14, $CHCl_3$). IR/cm^{-1}: 1750, 1734, 1373, 1218, 1037.

2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-1-thio-D-glucopyranose (20):



18 (15.0 g, 20.6 mmol) was co-evaporated with toluene (3 x), after which it was dissolved in dry MeOH (100 mL). A catalytic amount of NaOMe was added and the reaction mixture was stirred for two hours. TLC-MS analysis showed complete conversion of the starting material into a polar product. The mixture was diluted with MeOH after which amberlite H^+ was added until pH was adjusted to 7. After filtering and concentrating the deprotected sugar (**19**) was co-evaporated with toluene (3 x). **19** was dissolved in DMF (100 mL), BnBr (20.9 mL, 176 mmol) was added, the solution was cooled (0 °C). NaH (14.5 g, 360 mmol) was added in small portions, after which the solution was stirred overnight under argon atmosphere. TLC analysis showed complete consumption of the starting compound (1:1, PE:EtOAc). After cooled down to 0 °C, the reaction mixture was sequently quenched by the addition of MeOH, the volatiles evaporated and EtOAc (200 mL) was added. The mixture was washed with HCl solution (1M, 100 mL, 2 x). After being dried (Na_2SO_4), filtered, and concentrated, the crude product was purified with silica gel column chromatography (17:3 → 4:1 → 1:1, PE:EtOAc) to give **20** in 50% yield over the 2 steps (11.0 g, 10.3 mmol). R_F = 0.88 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.12 (m, 40H, H_{Ar} SPh/Bn), 5.03 (d, *J* = 3.5 Hz, 1H, H-1'), 4.66 (d, *J* = 9.9 Hz, 1H, H-1), 4.97 – 4.37 (m, 14H, 7 x CH_2 Bn), 4.05 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2'), 3.99 (t, *J* = 6.5 Hz, 1H, H-5), 3.89 (m, 1H, H-3'), 3.86 (d, *J* = 2.9 Hz, 1H, H-4'), 3.78 (qd, *J* = 11.7, 3.5 Hz, 2H, H_2-6'), 3.68 – 3.59 (m, 2H, H-3, H-4), 3.54 (dd, *J* = 9.3, 5.9 Hz, 1H, H-5'), 3.49 (dd, *J* = 9.5, 6.5 Hz, 2H, H_2-6), 3.26 (dd, *J* = 9.9, 8.5 Hz, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 – 138.1 (C_q Bn), 134.2 (C_q SPh), 131.9 – 127.5 (CH_{Ar} Bn), 97.9 (C-1'), 87.8 (C-1), 86.8 (C-3), 81.2 (C-2), 79.0 (C-5), 78.5 (C-4'), 78.0 (C-4), 76.9 (C-2), 75.8, 75.6 (2 x CH_2 Bn), 75.3 (C-3'), 75.1, 74.9, 73.4, 73.2, 72.8 (5 x CH_2 Bn), 72.8, 69.3 (C-5), 69.1 (C-6), 66.4 (C-6'). IR/cm^{-1}: 3088, 3063, 3030, 2905, 2866, 1454, 1352, 1094, 1040.

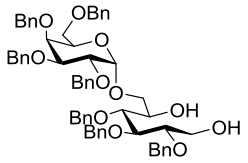
2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α/β-glucopyranose (21):



NIS (22 mg, 97 µmol) and 30 µL of TFA were added to a cooled solution of **20** (94 mg, 88 µmol) in 2 mL DCM at 0 °C. After an hour of stirring TLC, analysis (4:1, toluene:EtOAc) showed complete consumption of the starting material. Sat. aq. $Na_2S_2O_3$ solution (7 mL) followed by sat. aq. $NaHCO_3$ solution (7 mL) was added. The mixture was diluted with DCM, after 30 minutes of stirring the layers were separated. The organic layer was dried ($MgSO_4$) and after filtering and concentrating the crude product was purified on silica gel column chromatography (9:1 → 7:3 → 6:4, PE:EtOAc) to give **21** in 77% yield (70 mg, 68 µmol). R_F = 0.30 and 0.40 (7:3, PE:EtOAc). For the major anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 35H, H_{Ar} Bn), 5.09 (d, *J* = 3.6 Hz, 1H, H-1'), 4.98 (d, *J* = 3.5 Hz, 1H, H-1), 4.95 – 4.28 (m, 14H, 7 x CH_2 Bn), 4.13 (dt, *J* = 14.3, 6.8 Hz, 1H, H-5'), 4.07 – 3.98 (m, 2H, H-4, H-5), 3.96 – 3.88 (m, 3H, H-2', H-3, H-4'), 3.85 (d, *J* = 11.7 Hz, 1H, H-6'a), 3.72 (dd, *J* = 12.0, 5.5 Hz, 1H, H-6'b), 3.64 – 3.43 (m, 3H, H-2, H_2-6), 3.39 (dd, *J* = 9.4, 3.5 Hz, 1H, H-2), 3.26 (dd, *J* = 8.6, 7.3 Hz, 1H, H-3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.4, 138.3, 138.1, 137.9, 137.8 (7 x C_q Bn), 128.6 – 127.6 (CH_{Ar} Bn), 98.5 (C-1'), 91.1 (C-1), 83.6 (C-3'), 81.9 (C-3), 80.4 (C-4), 78.6 (C-2), 78.2 (C-2'), 76.7 (C-4'), 75.8 – 72.7 (7 x CH_2 Bn), 70.8 (C-5'), 69.6 (C-5), 69.6 (C-6), 67.8 (C-6'). $[\alpha]^{20}_D$ = +38.1 (c = 1.03, $CHCl_3$). IR/cm^{-1}: 3030, 2920, 2868, 2247, 1497, 1454, 1357, 1090, 1026. HRMS: found 995.43431 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 995.43408.

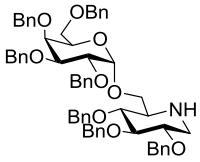
2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-D-glucitol (22):

$LiAlH_4$ in THF (6.0 mL, 2 M, 12.0 mmol) was slowly added to a cooled (0 °C) solution of **21** (3.91 g, 4.02 mmol, co-evaporated 3 x with toluene), in dry THF (40 mL) under argon atmosphere.



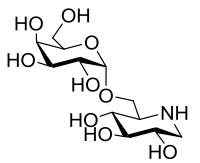
The mixture was stirred overnight allowing the temperature to reach r.t. TLC analysis showed absent of the starting compound (7:3, PE:EtOAc). The mixture was cooled in an ice-bath, after which it was slowly quenched by addition of H_2O. Then NaOH solution (3M, 40 mL) was added followed by Celite. The solution was stirred until a homogenous mixture was formed and after which it was filtered and the filter cake rinsed with Et_2O. H_2O (50 mL) and EtOAc (50 mL) was added and the organic layer was dried (Na_2SO_4), filtered and concentrated, the residue was purified with silica gel column chromatography (4:1 → 7:3 → 3:2, PE:EtOAc) to give **22** as an yellow oil in 74% yield (2.88 g, 2.95 mmol). R_F = 0.22 (7:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 35H, H_{Ar} Bn), 4.88 (d, *J* = 3.7 Hz, 1H, H-1'), 5.03 – 4.29 (m, 14H, 7 x CH_2 Bn), 4.06 (dd, *J* = 10.0, 3.6 Hz, 1H, H-2'), 4.02 – 3.93 (m, 3H, H-4', H-5, H-5'), 3.92 – 3.86 (m, 2H, H-3, H-3'), 3.82 (dd, *J* = 11.1, 5.3 Hz, 1H, H-6a), 3.73 (ddd, *J* = 20.7, 12.0, 4.8 Hz, 4H, H-4, H-1a, H-2, H-4', H-6b), 3.55 (dd, *J* = 11.3, 4.3 Hz, 1H, H-1b), 3.49 (d, *J* = 6.5 Hz, 2H, H_2-6'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 – 138.0 (C_q Bn), 128.6-127.5 (CH_{Ar} Bn), 99.0 (C-1'), 79.6 (C-3), 79.4 (C-4), 79.2 (C-2), 78.5 (C-3'), 76.5 (C-2'), 74.9, 74.9 (2 x CH_2 Bn), 74.8 (C-4'), 73.9 – 72.9 (5 x CH_2 Bn), 70.6 (C-6), 70.4 (C-5'), 69.8 (C-5), 69.0 (C-6'), 61.9 (C-1). $[\alpha]^{20}_D$ = +34.4 (c = 1.02, $CHCl_3$). IR/cm^{-1}: 3335, 2974, 2289, 1636, 1456, 1418, 1088, 1045. HRMS: found 997.44913 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 997.44973.

2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-α-D-galactopyranosyl)-1-deoxynojirimycin (23):



A solution of $(COCl)_2$ (1.2 mL, 14.0 mmol) in dry DCM (15 mL) under argon atmosphere, was cooled to -78 °C. DMSO (1.2 mL, 16.9 mmol) dissolved in dry DCM (12 mL) was added dropwise. After 40 minutes **22** (4.28 g, 3.22 mmol), which was co-evaporated with toluene (3 x), in dry DCM (18 mL), was added dropwise to the mixture. The reaction was stirred for 2 hours at -70 °C, after which Et_3N (5.4 mL, 38.7 mmol) was added dropwise. The mixture was gradually warmed to -5 °C after which it was poured into a cooled (0 °C) MeOH solution (200 mL) containing $NaCNBH_3$ (0.813 g, 12.3 mmol), $HCOONH_4$ (4.07 g, 64.5 mmol), and Na_2SO_4 (1.37 g, 9.67 mmol). The mixture was stirred overnight allowing the reaction to reach r.t. TLC analysis showed the formation of the product. After filtering, the solvents were evaporated, after which the residue was dissolved in EtOAc (200 mL). The solution was washed with sat. aq. $NaHCO_3$ solution (200 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated, the crude product was purified with silica gel column chromatography (4:1 → 7:3 → 3:2 → 1:1, PE:EtOAc) to give the **23** in 71% yield (2.17 g, 2.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 35H, H_{Ar} Bn), 4.91 (d, *J* = 3.7 Hz, 1H, H-1'), 5.05 – 4.26 (m, 14H, 7 x CH_2 Bn), 4.06 (dd, *J* = 10.0, 3.6 Hz, 1H H-2'), 3.97 (d, *J* = 2.7 Hz, 1H, H-4'), 3.94 – 3.87 (m, 2H, H-3', H-5'), 3.86 (dd, *J* = 10.5, 5.3 Hz, 1H, H-6a), 3.64 (dd, *J* = 10.5, 2.6 Hz, 1H, H-6b), 3.54 (dd, *J* = 9.1, 2.5 Hz, 1H, H-6'a), 3.53 (t, *J* = 9.0 Hz, 1H, H-3), 3.49 (dd, *J* = 9.3, 6.1 Hz, 1H, H-6'b), 3.32 (t, *J* = 9.2 Hz, 1H, H-2), 3.31 (t, *J* = 9.5, 1H, H-4), 2.95 (dd, *J* = 12.5, 5.1, 1H, H-1'a), 2.68 (ddd, *J* = 9.6, 5.2, 2.6, 1H, H-5), 2.37 (dd, *J* = 12.4, 10.7, 1H, H-1'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 – 137.9 (C_q Bn), 128.4 – 127.4 (CH_{Ar} Bn), 99.0 (C-1'), 87.2 (C-3), 80.9 (C-4), 80.0 (C-2), 78.8 (C-3'), 76.8 (C-2'), 75.6, 75.1, 74.7 (3 x CH_2 Bn), 74.7 (C-4'), 73.6, 73.4, 72.6, 72.6 (4 x CH_2 Bn), 69.6 (C-5'), 69.4 (C-6), 68.8 (C-6'), 59.5 (C-5), 47.7 (C-1). IR/cm^{-1}: 3032, 2899, 2872, 1497, 1453, 1354, 1208, 1093, 1059, 1027. $[\alpha]^{20}_D$ = +58.2 (c = 0.5, $CHCl_3$). HRMS: found 956.47363 $[C_{61}H_{66}NO_9+H]^+$, calculated for $[C_{61}H_{66}NO_9+H]^+$ 956.47321.

6-*O*-(α-D-Galactopyranosyl)-1-deoxynojirimycin (24):

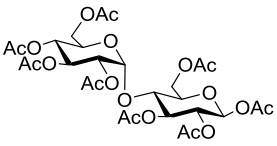


A mixture of DMF/MeOH (1:1, 20 mL), HCl (2 mL, 1M) and **23** (2.00 g, 2.09 mmol) was flushed with argon (3 x). Then a catalytic amount of Pd/C (20%) was added, after which H_2 was flushed through the mixture, and the solution shaken overnight under H_2 atmosphere (4 bar). HPLC analyses showed

complete conversion of starting material into the desired product. Then the catalyst was filtered and the solution was concentrated. The crude product was purified on size-exclusion column (NH_4HCO_3 in water 0.15 M). After co-evaporating (3 x) with Milli-Q water, product **24** was obtained as a white solid in 75% yield (326 mg, 1.00 mmol). ^{1}H NMR (400 MHz, MeOD) δ 4.84 (d, *J* = 3.4 Hz, 1H, H-1'), 4.01 (dd, *J* = 10.5, 4.7 Hz, 1H, H-6a), 3.90 (dd, *J* = 3.0, 1.2 Hz, 1H, H-4'), 3.84 (td, *J* = 6.1, 1.1 Hz, 1H, H-5'), 3.80 (dd, *J* = 10.1, 3.4 Hz, 1H, H-2'), 3.76 (dd, *J* = 10.1, 3.0 Hz, 1H, H-3'), 3.70 (d, *J* = 6.1 Hz, 2H, H_2-6'), 3.59 (dd, *J* = 10.4, 2.5 Hz, 1H, H-6b), 3.52 (ddd, *J* = 11.0, 9.1, 5.1 Hz, 1H, H-2), 3.38 (dd, *J* = 10.1, 9.0, 1H, H-4), 3.25 (t, *J* = 9.0 Hz, 1H, H-3), 3.20 (dd, *J* = 12.3, 5.1 Hz, 1H, H-1a), 2.82 (ddd, *J* = 10.0, 4.6, 2.6 Hz, 1H, H-5), 2.60 (dd, *J* = 12.3, 11.0 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 100.3 (C-1'), 79.9 (C-3), 72.4 (C-5'), 71.6 (C-4), 71.5 (C-2), 71.2 (C-3'), 70.9 (C-4'), 70.4 (C-2'), 66.8 (C-6), 62.6 (C-6'), 60.5 (C-5), 49.9 (C-1). $[\alpha]^{20}_D$ = +92.8 (c = 1.0, MeOH). IR/cm^{-1}: 3482, 2928, 2962, 1653, 1506, 1409, 1437, 1387, 1255, 1092, 1063. HRMS: found 326.14465 $[C_{12}H_{23}NO_9+H]^+$, calculated for $[C_{12}H_{23}NO_9+H]^+$ 326.14456.

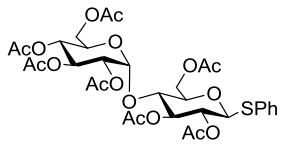
Synthesis of 4-*O*-α-D-glucopyranosyl-1-deoxynojirimycin (33)

1,2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-glucopyranose (26):



A suspension of Ac_2O (59.0 mL, 0.625 mol) and NaOAc (4.33 g, 52.8 mmol) was heated to reflux in an oil bath. When refluxing began the heat source was removed and maltose (9.94 g, 29.0 mmol, co-evaporated with toluene 3 x) was added in small portions. The mixture was heated again to reflux and after an hour, TLC analysis confirmed the formation of the product (1:1, PE:EtOAc, R_F = 0.36). The mixture was poured into ice water (400 mL) which was vigorously stirred. DCM (150 mL) was added and the layers were separated after which the organic layer was washed with water (200 mL), sat. aq. $NaHCO_3$ solution (2 x 150 mL) and brine (200 mL). After the organic layer was dried (Na_2SO_4), filtered, and concentrated, the residue was purified with silica gel column chromatography (1:1 → 1:2 → 0:1, PE:EtOAc) to give the pure **26** in 94% yield (18.5 g, 27.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 8.2 Hz, 1H, H-1), 5.42 (dd, *J* = 12.4, 4.0 Hz, 1H, H-1'), 5.36 (dd, *J* = 9.8, 2.3 Hz, 1H, H-3), 5.33 – 5.26 (m, 1H, H-3'), 5.11 – 4.94 (m, 2H, H-4', H-2), 4.86 (ddd, *J* = 10.5, 6.2, 4.0 Hz, 1H, H-2'), 4.45 (dd, *J* = 12.3, 2.4 Hz, 1H, H-6'a), 4.27 – 4.19 (m, 2H, H-6a, H-6'b), 4.14 – 4.08 (m, 1H, H-6b), 4.04 (ddd, *J* = 8.9, 5.8, 3.8 Hz, 1H, H-4), 3.96 – 3.91 (m, 1H, H-5'), 3.84 (ddd, *J* = 9.6, 4.3, 2.5 Hz, 1H, H-5), 2.26 – 1.96 (m, 24H, 8 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 – 168.9 (8 x C=O), 95.8 (C-1'), 91.3 (C-1), 75.3 (C-3'), 73.0 (C-5), 72.4 (C-4), 71.0 (C-2), 70.1 (C-2'), 69.3 (C-3), 68.6 (C-5'), 68.0 (C-4'), 62.6 (C-6'), 61.5 (C-6), 20.9 – 20.6 (8 x CH_3).

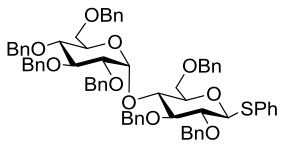
2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-D-glucopyranose (27):



27 was synthesised from **26** (18.5 g, 27.3 mmol) according to the procedure described for the preparation for compound **18**, to gain **27** (12.1 g, 16.5 mmol, 61% yield) as a colourless oil. R_F = 0.43 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H, H_{Ar} SPh), 7.36 – 7.28 (m, 3H, H_{Ar} SPh), 5.39 (d, *J* = 4.0 Hz, 1H, H-1'), 5.34 (dd, *J* = 10.5, 9.6 Hz, 1H, H-3), 5.28 (t, *J* = 8.9 Hz, 1H, H-3'), 5.04 (t, *J* = 9.9 Hz, 1H, H-4'), 4.85 (dd, *J* = 10.5, 4.0 Hz, 1H, H-2'), 4.79 (d, *J* = 9.0 Hz, 1H, H-2), 4.73 (d, *J* = 10.1 Hz, 1H, H-1), 4.54 (dd, *J* = 12.1, 2.5 Hz, 1H, H-6'a), 4.24 (dd, *J* = 10.5, 4.5 Hz, 1H, H-6a), 4.21 (dd, *J* = 10.2, 4.4 Hz, 1H, H-6'b), 4.04 (dd, *J* = 10.2, 4.4 Hz, 1H, H-6b), 3.95 (dd, *J* = 9.7, 9.0 Hz, 1H, H-4), 3.94 (ddd, *J* = 10.4, 4.0, 2.4 Hz, 1H, H-5'), 3.72 (ddd, *J* = 9.8, 4.8, 2.6 Hz, 1H, H-5), 2.14 – 1.99 (m, 21H, 7 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 – 169.6 (C=O), 133.5 (C_{Ar} SPh), 131.4 (C_q SPh), 129.0, 128.6 (C_{Ar} SPh), 95.7 (C-1'), 85.2 (C-1), 76.6 (C-3'), 76.2 (C-5), 72.5 (C-4), 70.8 (C-2), 70.1 (C-2'), 69.4 (C-3), 68.6

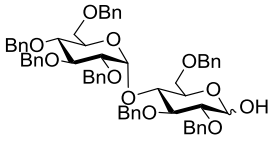
(C-5'), 68.1 (C-4'), 62.9 (C-6'), 61.6 (C-6), 21.1 – 20.7 (CH_3). $[\alpha]^{20}_D$ = +30.6 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 1746, 1368, 1223, 1038, 912.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-thio-D-glucopyranose (29):



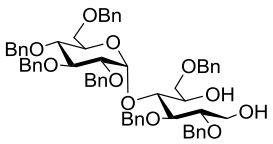
29 was synthesised from **27** (11.9 g, 13.3 mmol) according to the procedure described for the preparation for compound **19**, to gain **29** (15.4 g, 14.5 mmol, 89% yield) as a light yellow oil. R_F = 0.63 (4:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.5, 3.0 Hz, 2H, H_{Ar} SPh), 7.33 – 7.16 (m, 32H, H_{Ar} Bn, H_{Ar} SPh), 7.13 – 7.08 (m, 6H, H_{Ar} Bn), 5.64 (d, *J* = 3.6 Hz, 1H, H-1'), 4.92 – 4.76 (m, 6H, 3 x CH_2 Bn), 4.70 (d, *J* = 9.7 Hz, 1H, H-1), 4.62 – 4.41 (m, 7H, 7 x CH*H* Bn), 4.31 (d, *J* = 12.1 Hz, 1H, CH*H* Bn), 4.12 (t, *J* = 9.2 Hz, 1H, H-4), 3.93 (dd, *J* = 9.9, 8.9 Hz, 1H, H-3'), 3.89 (dd, *J* = 11.3, 4.3 Hz, 1H, H-6'a), 3.83 (dd, *J* = 6.5, 4.3 Hz, 1H, H-6'b), 3.82 (t, *J* = 8.8 Hz, 1H, H-3), 3.79 (dd, *J* = 7.3, 2.7 Hz, 1H, H-5'), 3.67 (dd, *J* = 17.1, 8.0 Hz, 1H, H-4'), 3.60 (dd, *J* = 11.2, 1.8 Hz, 1H, H-6a), 3.59 (dd, *J* = 10.5, 3.3 Hz, 1H, H-5), 3.58 (t, *J* = 10.2 Hz, 1H, H-2), 3.51 (dd, *J* = 9.9, 3.7 Hz, 1H, H-2'), 3.45 (dd, *J* = 10.6, 1.8 Hz, 1H, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 – 137.8 (7 x C_q Bn), 133.7 (C_q SPh), 132.0 – 126.5 (C_{Ar} SPh), 97.1 (C-1'), 87.2 (C-1), 86.7 (C-3), 82.0 (C-3'), 80.9 (C-2), 79.4 (C-2'), 78.8 (C-5), 77.7 (C-4'), 75.5 – 73.3 (7 x CH_2Bn), 72.7 (C-4), 71.1 (C-5'), 69.2 (C-6'), 68.3 (C-6). $[\alpha]^{20}_D$ = + 2.87 (c = 2.31, $CHCl_3$). IR/cm^{-1}: 3063, 3030, 2904, 2864, 1452, 1360, 1207, 1140, 1084, 1055, 1026.

2,3,6-Tri-O-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α/β-glucopyranose (30):



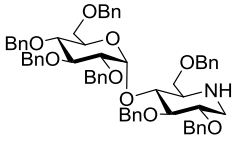
30 was synthesised from **29** (14.5 g, 13.6 mmol) according to the procedure described for the preparation for compound **21**, to gain **30** (12.3 g, 12.3 mmol, 93% yield) as a light yellow oil. R_F = 0.40 and 0.30 (7:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.07 (m, 35H, H_{Ar} Bn), 5.66 (dd, *J* = 8.6, 3.6 Hz, 1H, H-1'), 5.21 (t, *J* = 2.9 Hz, 1H, H-1), 5.02 – 4.26 (m, 14H, 7 x CH_2 Bn), 4.31 (dd, *J* = 12.2, 10.0 Hz, 1H, H-4), 4.13 (t, *J* = 8.8 Hz, 1H, H-3), 4.03 – 3.82 (m, 2H, H-3', H-5), 3.80 – 3.58 (m, 5H, H-2, H-4', H-5', H_2-6'), 3.55 – 3.45 (m, 2H, H-2', H-6a), 3.39 (ddd, *J* = 10.7, 3.6, 1.7 Hz, 1H, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.7, 138.4, 138.2, 138.0, 137.9, 137.7 (7 x C_q Bn), 128.4 – 127.1 (CH_{Ar} Bn), 96.9 (C-1'), 90.7 (C-1), 82.0 (C-3'), 81.4 (C-4), 80.0 (C-2), 79.4 (C-2'), 77.7 (C-4'), 75.6 – 72.9 (7 x CH_2 Bn), 72.9 (C-3), 71.1 (C-5), 69.6 (C-5'), 69.2 (C-6'), 68.1 (C-6). $[\alpha]^{20}_D$ = +32.8 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 3418, 3063, 3030, 2903, 2864, 1497, 1452, 1362, 1265, 1207, 1146, 1088, 1043, 1026.

2,3,6-Tri-O-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-glucitol (31):



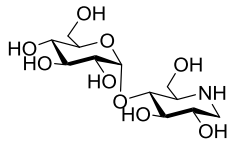
31 was synthesised from **30** (11.3 g, 11.6 mmol) according to the procedure described for the preparation for compound **22**, to gain **31** (8.33 g, 8.55 mmol, 74% yield) as a light yellow oil. R_F = 0.31 (7:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.07 (m, 35H, H_{Ar} Bn), 4.82 (d, *J* = 3.1 Hz, 1H, H-1'), 4.96 – 4.35 (m, 14H, 7 x CH_2 Bn), 4.12 (dd, *J* = 8.6, 4.0 Hz, 1H, H-3'), 3.98 (ddd, *J* = 10.2, 3.2, 2.1 Hz, 1H, H-5), 3.96 – 3.90 (m, 4H, H-5', H-4, H-3', H-4'), 3.71 (dt, *J* = 29.8, 6.9 Hz, 2H, H-1), 3.60 – 3.53 (m, 6H, H_2-6, H_2-6', H-2, H-2'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 – 137.6 (C_q Bn), 129.1 – 125.4 (CH_{Ar} Bn), 99.2 (C-1'), 82.0 (C-3), 79.9 (C-3'), 79.7 (C-4'), 79.4 (C-2), 78.8 (C-4), 77.8 (C-2'), 75.7 – 72.8 (7 x CH_2 Bn), 71.8 (C-3'), 71.6 (C-6), 71.2 (C-5), 68.3 (C-6'), 61.6 (C-1). $[\alpha]^{20}_D$ = +38.1 (c = 1.03, $CHCl_3$). IR/cm^{-1}: 3420, 3063, 3030, 2862, 1454, 1207, 1086, 1070, 1028. HRMS: found 997.44970 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 997.44973.

2,3,6-Tri-O-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-deoxynojirimycin (32):



32 was synthesised from **31** (0.998 g, 1.02 mmol) according to the procedure described for the preparation for compound **23**, to gain **32** (0.428 g, 0.448 mmol, 44% yield) as a light yellow oil. R_F = 0.38 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.26 (m, 35H, H_{Ar} Bn), 5.94 (d, *J* = 3.6 Hz, 1H, H-1'), 5.30 – 4.46 (m, 14H, CH_2 Bn), 4.11 (dd, *J* = 9.8, 8.5 Hz, 1H, H-3'), 3.98 (dd, *J* = 9.5, 8.7 Hz, 1H, H-4), 3.93 – 3.87 (m, 2H, H-5', H-6a), 3.88 (t, *J* = 8.7 Hz, 1H, H-3), 3.84 (dd, *J* = 8.7, 1.3 Hz, 1H, H-4'), 3.81 (dd, *J* = 8.7, 5.6 Hz, 1H, H-6b), 3.73 (dd, *J* = 10.6, 2.8 Hz, 1H, H-6'a), 3.73 – 3.70 (m, 1H, H-2), 3.67 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2'), 3.61 (dd, *J* = 10.4, 1.3 Hz, 1H, H-6'b), 3.42 (dd, *J* = 12.3, 5.1 Hz, 1H, H-1a), 3.03 (ddd, *J* = 9.1, 5.8, 2.9, 1H, H-5), 2.70 (dd, *J* = 12.3, 10.6 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 – 137.9 (7 x C_q Bn), 128.3 – 126.5 (CH_{Ar} Bn), 96.6 (C-1'), 87.0 (C-3), 82.0 (C-3'), 80.9 (C-2), 79.3 (C-2'), 77.7 (C-4'), 75.5, 74.9 (2 x CH_2 Bn), 74.2 (C-4), 73.8 – 72.5 (5 x CH_2 Bn), 71.0 (C-5'), 70.5 (C-6), 68.1 (C-6'), 59.0 (C-5), 47.8 (C-1). $[\alpha]^{20}_D$ = +26.0 (c = 0.7, $CHCl_3$). IR/cm^{-1}: 2918, 2866, 1454, 1362, 1740, 1090, 1072, 1047, 1026. HRMS: found 956.47311 $[C_{61}H_{66}NO_9+H]^+$, calculated for $[C_{61}H_{66}NO_9+H]^+$ 956.47321.

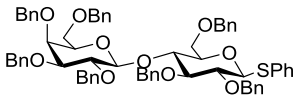
4-*O*-(α-D-Glucopyranosyl)-1-deoxynojirimycin (33):



33 was synthesised from **32** (1.00 g, 1.04 mmol) according to the procedure described for the preparation for compound **24**, to gain **33** (0.24 g, 0.74 mmol, 71% yield) as a light yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 5.21 (d, *J* = 3.7 Hz, 1H, H-1'), 4.00 (dd, *J* = 12.1, 4.8 Hz, 1H, H-6a), 3.91 (dd, *J* = 12.0, 3.0 Hz, 1H, H-6b), 3.88 – 3.83 (m, 1H, H-6'a), 3.77 (ddd, *J* = 4.8, 8.9, 10.8 Hz, 1H, H-2). 3.81 – 3.66 (m, 4H, H-3', H-4', H-6'b, H-3), 3.62 (dd, *J* = 9.7, 9.0 Hz, 1H, H-4) 3.49 (dd, *J* = 9.7, 3.8 Hz, 1H, H-2'), 3.35 (dd, *J* = 12.5, 5.0 Hz, 1H, H-1a), 3.30 – 3.23 (m, 2H, H-5', H-5), 2.91 (dd, *J* = 12.4, 10.9 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 103.1 (C-1'), 79.3 (C-3'), 77.7 (C-3), 75.1 (C-4'), 74.9 (C-4), 73.9 (C-2'), 71.4 (C-5'), 68.2 (C-2), 62.7 (C-6'), 60.5 (C-5), 58.8 (C-6), 47.1 (C-1). $[\alpha]^{20}_D$ = +25.0 (c =0.2, MeOH). IR/cm^{-1}: 3303, 2967, 1636, 1560, 1203, 1161, 1022. HRMS: found 326.14464 $[C_{12}H_{23}NO_9+H]^+$, calculated for $[C_{12}H_{23}NO_9+H]^+$ 326.14456.

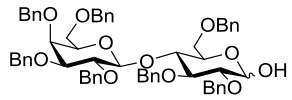
Synthesis of β-D-galactopyranosyl-1-deoxynojirimycin (40)

2,3,6-Tri-*O*-benzyl-4-(2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl)-1-thio-D-glucopyranose (36):



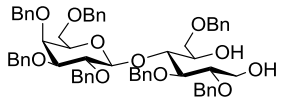
36 was synthesised from **34** (3.64 g, 5.00 mmol) according to the procedure described for the preparation for compound **20**, to gain **36** (5.32 g, 5.00 mmol, 100% yield) as a light yellow oil. R_F = 0.67 (4:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.04 (m, 40H, H_{Ar} Bn/SPh), 4.67 (d, *J* = 10.5 Hz, 1H, H-1), 5.13 – 4.20 (m, 14H, 7 x CH_2 Bn), 4.45 (d, *J* = 7.7 Hz, 1H, H-1'), 4.00 – 3.91 (m, 2H, H-4', H-5'), 3.82 (dd, *J* = 11.0, 4.3 Hz, 1H, H-6'a), 3.79 – 3.73 (m, 2H, H-2', H-6'b), 3.61 (t, *J* = 8.9 Hz, 1H, H-3'), 3.52 (t, *J* = 7.6 Hz, 1H, H-6a), 3.47 – 3.31 (m, 5H, H-2, H-3, H-4, H-5 H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 – 138.2 (7 x C_q Bn), 133.8 (C_q SPh), 132.2 – 127.3 (CH_{Ar} Bn/SPh), 103.0 (C-1'), 87.5 (C-1), 85.1 (C-3'), 82.7 (C-4), 80.2 (C-2), 80.1 (C-2'), 79.5 (C-3), 76.6 (C-4'), 75.7, 75.6, 75.5, 74.5 (4 x CH_2 Bn), 73.7 (C-5'), 73.5, 73.2 (2 x CH_2 Bn), 73.1 (C-5), 72.2 (CH_2 Bn), 68.5 (C-6'), 68.2 (C-6). IR/cm^{-1}: 3030, 2920, 2862, 1497, 1454, 1362, 1209, 1088, 1076, 1028, 1001.

2,3,6-Tri-*O*-benzyl-4-(2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl)-α/β-D-glucopyranose (37):



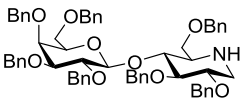
37 was synthesised from **36** (0.12 g, 0.12 mmol) according to the procedure described for the preparation for compound **21**, to gain **37** (96.0 mg, 98.7 µmol, 85% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.04 (m, 40H, H_{Ar} Bn/SPh), 5.16 (d, *J* = 3.7 Hz, 1H, H-1), 5.10 – 4.17 (m, 14H, 7 x CH_2 Bn), 4.33 (d, *J* = 9.4 Hz, 1H, H-1'), 3.99 – 3.87 (m, 3H, H-2', H-3', H-5'), 3.87 – 3.80 (m, 2H, H-4, H-3), 3.74 (ddd, *J* = 10.0, 7.5, 2.4 Hz, 1H, H-6'a), 3.65 (dd, *J* = 10.5, 1.6 Hz, 1H, H-6'b), 3.52 (ddd, *J* = 12.7, 9.3, 6.7 Hz, 2H, H-2, H-6a), 3.42 – 3.29 (m, 4H, H-3, H-4', H-5, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3 – 138.1 (C_q Bn), 128.5 – 127.2 (CH_{Ar} Bn), 103.0 (C-1'), 91.5 (C-1), 82.5 (C-3), 80.0 (C-2), 79.2 (C-2'), 76.6 (C-3'), 75.5, 72.3 (2 x CH_2 Bn), 75.1 (C-4'), 74.8 (CH_2 Bn), 73.8 (C-4), 73.7, 73.6, 73.2 (3 x CH_2 Bn), 73.2 (C-5'), 72.7 (CH_2 Bn), 70.5 (C-5), 68.3 (C-6'), 68.1 (C-6). $[\alpha]^{20}_D$ = +12.4 (c = 1.07, $CHCl_3$). IR/cm^{-1}: 2920, 2864, 1452, 1396, 1362, 1207, 1090. HRMS: found 995.43425 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 995.43408.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-D-glucitol (38):



38 was synthesised from **37** (5.44 g, 5.59 mmol) according to the procedure described for the preparation for compound **22**, to gain **38** (4.17 g, 4.28 mmol, 77% yield) as a light yellow oil. R_F = 0.20 (7:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 35H, H_{Ar} Bn), 4.97 – 4.22 (m, 14H, 7 x CH_2 Bn), 4.34 (dd, *J* = 7.2, 5.4 Hz, 1H, H-1'), 4.03 (dd, *J* = 7.4, 2.4 Hz, 1H, H-4), 3.99 (dt, *J* = 7.9, 3.8 Hz, 2H, H-2, H-5'), 3.95 (dd, *J* = 7.8, 2.4 Hz, 1H, H-3), 3.83 (d, *J* = 2.9 Hz, 1H, H-4'), 3.77 (dd, *J* = 9.8, 7.7 Hz, 1H, H-2'), 3.71 (dd, *J* = 6.9, 3.7, 2H, H-1), 3.66 (dd, *J* = 9.9, 4.4 Hz, 1H, H-6'a), 3.55 (dd, *J* = 9.8, 3.0 Hz, 1H, H-6'b), 3.48 (dd, *J* = 6.3, 2.5 Hz, 2H, H_2-6), 3.42 (dd, *J* = 10.0, 6.4 Hz, 1H, H-5), 3.40 (dd, *J* = 9.7, 3.0 Hz, 1H, H-3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 – 137.7 (C_q Bn), 128.5 – 127.3 (CH_{Ar} Bn), 103.8 (C-1'), 82.42 (C-3'), 79.9 (C-4), 79.8 (C-2), 79.4 (C-2'), 77.5 (C-3), 75.4, 74.9, 74.7 (3 x CH_2 Bn), 73.8 (C-4'), 73.6, 73.3 (2 x CH_2 Bn), 73.3 (C-5), 73.2, 73.0 (2 x CH_2 Bn), 70.8 (C-5'), 70.8 (C-6'), 68.9 (C-6), 62.3 (C-1). IR/cm^{-1}: 3028, 2922, 2864, 1063, 1026, 1001. $[\alpha]^{20}_D$ = +6.6 (c = 1.0, $CHCl_3$). HRMS: found 997.44976 $[C_{61}H_{66}O_{11}+Na]^+$, calculated for $[C_{61}H_{66}O_{11}+Na]^+$ 997.44973.

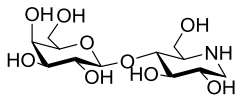
2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-1-deoxynojirimycin (39):



39 was synthesised from **38** (4.17 g, 4.28 mmol) according to the procedure described for the preparation for compound **23**, to gain **39** (0.90 g, 0.94 mmol, 22% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.09 (m, 35H, H_{Ar} Bn), 5.05 (d, *J* = 10.7 Hz, 1H, CH*H* Bn), 4.98 (d, *J* = 11.4 Hz, 1H), 4.85 (d, *J* = 11.4 Hz, 1H, CH*H* Bn), 4.83 (d, *J* = 2.6 Hz, 2H, CH_2 Bn), 4.75 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.71 (d, *J* = 11.6 Hz, 2H, CH_2 Bn), 4.67 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.57 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.44 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.38 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.35 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.34 (d, *J* = 7.7 Hz, 1H, H-1'), 4.30 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 3.92 (d, *J* = 3.0 Hz, 1H, H-4'), 3.78 (dd, *J* = 9.7, 7.7 Hz, 1H, H-2'), 3.70 (dd, *J* = 9.0, 2.8 Hz, 1H, H-6a), 3.65 (dd, *J* = 9.4, 6.1 Hz, 1H, H-6b), 3.57 (dd, *J* = 9.8, 5.0 Hz, 1H, H-2), 3.52 (dd, *J* = 14.3, 7.4 Hz, 1H, H-6'a), 3.46 – 3.41 (m, 3H, H-5', H-3, H-4). 3.42 (dd, *J* = 9.8, 2.9 Hz, 1H, H-3'), 3.35 (dd, *J* = 14.0, 7.3 Hz, 1H, H-6'b), 3.20 (dd, *J* = 12.2, 4.5 Hz, 1H, H-1a), 2.71 (ddd, *J* = 9.2, 5.6, 2.6 Hz, 1H, H-5), 2.50 (dd, *J* = 12.2, 10.0 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 – 137.7 (C_q Bn), 128.6 – 127.6 (CH_2 Bn), 103.9 (C-1'), 82.5 (C-4'), 80.0 (C-5'), 79.8 (C-2'), 79.4 (C-3'), 77.6 – 74.7 (3 x CH_2 Bn), 73.7 (C-3), 73.6 (CH_2 Bn), 73.3 (C-5), 73.3 – 72.9 (3 x CH_2 Bn), 70.8 (C-2), 70.8 (C-6), 68.9 (C-6'), 62.3 (C-1). IR/cm^{-1}: 3060, 3029, 2916, 2866, 1497, 1453, 1361, 1208, 1097,

1028. $[\alpha]^{20}_D$ = +14.0 (c = 0.4, $CHCl_3$). HRMS: found 956.47340 $[C_{61}H_{66}O_9N$ +Na$]^+$, calculated for $[C_{61}H_{66}O_9N$+H$]^+$ 956.47321.

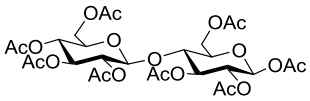
4-(β-D-Galactopyranosyl)-1-deoxynojirimycin (40):



40 was synthesised from **39** (0.932 g, 0.975 mmol) according to the procedure described for the preparation for compound **24**, to gain **40** (0.20 g, 0.621 mmol, 64% yield) as a light yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 4.44 (d, *J* = 7.6 Hz, 1H, H-1'), 3.92 (d, *J* = 3.7 Hz, 2H, H_2-6), 3.92 (d, *J* = 3.2, Hz, 1H, H-4'), 3.87 (dd, *J* = 11.4, 7.4 Hz, 1H, H-6'a), 3.79 (dd, *J* = 11.4, 4.7 Hz, 1H, H-6'b), 3.67 (ddd, *J* = 7.4, 4.7, 1.1 Hz, 1H, H-5'), 3.65 (dd, *J* = 9.8, 7.6 Hz, 1H, H-2'), 3.58 (dd, *J* = 9.7, 3.3 Hz, 1H, H-3'), 3.55 (ddd, *J* = 10.7, 9.1, 5.1 Hz, 1H, H-2), 3.50 (dd, *J* = 9.5, 8.8 Hz, 1H, H-4), 3.44 (t, *J* = 8.7 Hz, 1H, H-3), 3.17 (dd, *J* = 12.4, 5.1 Hz, 1H, H-1a), 2.71 (dt, *J* = 9.6, 3.8 Hz, 1H, H-5), 2.54 (dd, *J* = 12.5, 10.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 106.1 (C-1'), 83.6 (C-4), 79.6 (C-3), 77.9 (C-5'), 75.7 (C-3'), 73.5 (C-2), 73.3 (C-2'), 71.1 (C-4'), 63.3 (C-6'), 62.8 (C-6), 62.5 (C-5), 51.3 (C-1). $[\alpha]^{20}_D$ = +16.0 (c = 0.2, MeOH). IR/cm^{-1}: 3306, 2945, 2833, 1653, 1448, 1410, 1113, 1018. HRMS: found 326.14482 $[C_{12}H_{23}NO_9$+H$]^+$, calculated for $[C_{12}H_{23}NO_9$+H$]^+$ 326.14456.

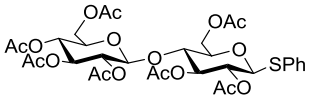
Synthesis of 4-*O*-(β-D-glucopyranosyl)-1-deoxynojirimycin (49)

2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-D-glucopyranose (42):



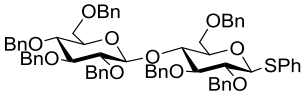
42 was synthesised from D-(+)-cellobiose (10.0 g, 29.2 mmol) according to the procedure described for the preparation for compound **17**, to gain **42** (19.5 g, 28.8 mmol, 98% yield). R_F = 0.36 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, *J* = 8.2 Hz, 1H, H-1), 5.23 (t, *J* = 9.2 Hz, 1H, H-3'), 5.18 – 4.99 (m, 3H, H-3, H-4, H-2), 4.97 – 4.87 (m, 1H, H-2'), 4.52 – 4.47 (m, 2H, H-6'a, H-1'), 4.37 (dd, *J* = 12.3, 4.4 Hz, 1H, H-6a), 4.12 (dd, *J* = 12.2, 4.6 Hz, 1H, H-6'b), 4.05 (dd, *J* = 12.5, 2.1 Hz, 1H, H-6b), 3.82 (dd, *J* = 15.6, 6.5 Hz, 1H, H-4'), 3.75 (ddd, *J* = 9.8, 4.7, 1.8 Hz, 1H, H-5), 3.66 (ddd, *J* = 9.9, 4.4, 2.4 Hz, 1H, H-5'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 – 169.0 (8 x C=O), 100.8 (C-1'), 91.7 (C-1), 76.0 (C-5'), 73.6 (C-4'), 73.0 (C-3'), 72.5 (C-3), 72.1 (C-5), 71.6 (C-2'), 70.5 (C-2), 67.9 (C-4), 61.7 (C-6'), 61.7 (C-6), 21.0 – 20.6 (8 x CH_3).

2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-D-glucopyranose (43):



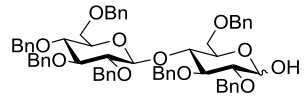
43 was synthesised from **42** (0.68 g, 1.00 mmol) according to the procedure described for the preparation for compound **18**, to gain **43** (0.67 g, 0.91 mmol, 91% yield) as a colourless oil. R_F = 0.53 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (dd, *J* = 10.4, 8.0 Hz, 1H, H-3'), 5.15 (dd, *J* = 9.4, 7.2 Hz, 1H, H-3), 5.06 (t, *J* = 9.7 Hz, 1H, H-4), 4.91 (ddd, *J* = 10.0, 8.6, 3.7 Hz, 2H, H-2, H-2'), 4.70 (d, *J* = 10.1 Hz, 1H, H-1'), 4.56 (dd, *J* = 11.9, 2.0 Hz, 1H, H-6'a), 4.54 (d, *J* = 7.9 Hz, 1H, H-1), 4.38 (dd, *J* = 12.5, 4.3 Hz, 1H, H-6a), 4.11 (td, *J* = 7.1, 1.9 Hz, 1H, H-6'b), 4.03 (dd, *J* = 12.4, 2.0 Hz, 1H, H-6b), 3.75 (m, 1H, H-4'), 3.69 (ddd, *J* = 8.9, 3.9, 1.8 Hz, 1H, H-5), 3.65 (dd, *J* = 5.7, 2.0 Hz, 1H, H-5'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 – 168.8 (7 x C=O), 132.8 (C_{Ar} SPh), 131.7 (C_q SPh), 128.7, 128.1 (C_{Ar} SPh), 100.5 (C-1'), 85.2 (C-1), 76.6 (C-5'), 76.2 (C-4'), 73.4 (C-3'), 72.8 (C-3), 71.7 (C-5), 71.4 (C-2'), 70.0 (C-2), 67.6 (C-4), 61.9 (C-6'), 61.4 (C-6), 20.9 – 20.3 (7 x CH_3). $[\alpha]^{20}_D$ = +30.6 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 2958, 2872, 1743, 1440, 1368, 1216, 1168, 1038. HRMS: found 751.18783 $[C_{32}H_{40}O_{17}S$+Na$]^+$, calculated for $[C_{32}H_{40}O_{17}S$+Na$]^+$ 751.18784.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-thio-D-glucopyranose (45):



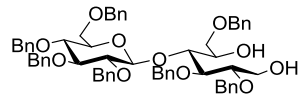
45 was synthesised from **43** (11.9 g, 13.3 mmol) according to the procedure described for the preparation for compound **19**, to gain **45** (15.4 g, 14.5 mmol, 89% yield) as a light yellow oil. R_F = 0.63 (4:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.5, 3.0 Hz, 2H, H_{Ar} SPh), 7.33 – 7.16 (m, 32H, H_{Ar} Bn, H_{Ar} SPh), 7.13 – 7.08 (m, 6H, H_{Ar} Bn), 5.64 (d, *J* = 3.6 Hz, 1H, H-1'), 4.92 – 4.76 (m, 6H, 3 x CH_2 Bn), 4.70 (d, *J* = 9.7 Hz, 1H, H-1), 4.62 – 4.41 (m, 7H, 7 x CH*H* Bn), 4.31 (d, *J* = 12.1 Hz, 1H, CH*H* Bn), 4.12 (t, *J* = 9.2 Hz, 1H, H-4), 3.93 (dd, *J* = 9.9, 8.9 Hz, 1H, H-3'), 3.89 (dd, *J* = 11.3, 4.3 Hz, 1H, H-6a'), 3.83 (dd, *J* = 6.5, 4.3 Hz, 1H, H-6b'), 3.82 (t, *J* = 8.8 Hz, 1H, H-3), 3.79 (dd, *J* = 7.3, 2.7 Hz, 1H, H-5'), 3.67 (dd, *J* = 17.1, 8.0 Hz, 1H, H-4'), 3.60 (dd, *J* = 11.2, 1.8 Hz, 1H, H-6a), 3.59 (dd, *J* = 10.5, 3.3 Hz, 1H, H-5), 3.58 (t, *J* = 10.2 Hz, 1H, H-2), 3.51 (dd, *J* = 9.9, 3.7 Hz, 1H, H-2'), 3.45 (dd, *J* = 10.6, 1.8 Hz, 1H, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 – 137.8 (7 x C_q Bn), 133.7 (C_q SPh), 132.0-126.5 (C_{Ar}), 97.1 (C-1'), 87.2 (C-1), 86.7 (C-3), 82.0 (C-3'), 80.9 (C-2), 79.4 (C-2'), 78.8 (C-5), 77.7 (C-4'), 75.5 – 73.3 (7 x CH_2Bn), 72.7 (C-4), 71.1 (C-5'), 69.2 (C-6'), 68.3 (C-6). $[\alpha]^{20}_D$ = + 2.87 (c = 2.31, $CHCl_3$). IR/cm^{-1}: 3063, 3030, 2904, 2864, 1452, 1360, 1207, 1140, 1084, 1055, 1026. HRMS: found 1087.44289 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 1087.44254.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α/β-glucopyranose (46):



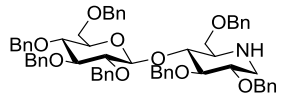
46 was synthesised from **45** (14.5 g, 13.6 mmol) according to the procedure described for the preparation for compound **21**, to gain **46** (12.3 g, 12.3 mmol, 90% yield) as a light yellow oil. R_F = 0.40 and 0.30 (7:3, PE:EtOAc). For the major anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.07 (m, 35H, H_{Ar} Bn), 5.66 (dd, *J* = 8.6, 3.6 Hz, 1H, H-1'), 5.21 (t, *J* = 2.9 Hz, 1H, H-1), 5.02 – 4.26 (m, 14H, 7 x CH_2 Bn), 4.31 (dd, *J* = 12.2, 10.0 Hz, 1H, H-4), 4.13 (t, *J* = 8.8 Hz, 1H, H-3), 4.03 – 3.82 (m, 2H, H-3', H-5), 3.80 – 3.58 (m, 5H, H-2, H-4', H-5', H_2-6'), 3.55 – 3.45 (m, 2H, H-2', H-6a), 3.39 (ddd, *J* = 10.7, 3.6, 1.7 Hz, 1H, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9 – 137.7 (7 x C_q Bn), 128.4 – 127.1 (CH_{Ar} Bn), 96.9 (C-1'), 90.7 (C-1), 82.0 (C-3'), 81.4 (C-4), 80.0 (C-2), 79.4 (C-2'), 77.7 (C-4'), 75.6 – 72.9 (7 x CH_2 Bn), 72.9 (C-3), 71.1 (C-5), 69.6 (C-5'), 69.2 (C-6'), 68.1 (C-6). $[\alpha]^{20}_D$ = +32.8 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 3418, 3063, 3030, 2903, 2864, 1497, 1452, 1362, 1265, 1207, 1146, 1088, 1043, 1026. HRMS: found 995.43387 $[C_{61}H_{64}O_{11}+Na]^+$, calculated for $[C_{61}H_{64}O_{11}+Na]^+$ 995.43408.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-glucitol (47):



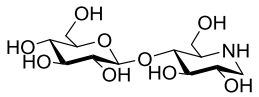
47 was synthesised from **46** (11.2 g, 11.6 mmol) according to the procedure described for the preparation for compound **22**, to gain **47** (8.33 g, 8.55 mmol, 74% yield) as a light yellow oil. R_F = 0.31 (7:3 PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.07 (m, 35H, H_{Ar} Bn), 4.82 (d, *J* = 3.1 Hz, 1H, H-1'), 4.96 – 4.35 (m, 14H, 7 x CH_2 Bn), 4.12 (dd, *J* = 8.6, 4.0 Hz, 1H, H-3'), 3.98 (ddd, *J* = 10.2, 3.2, 2.1 Hz, 1H, H-5), 3.96 – 3.90 (m, 4H, H-5', H-4, H-3', H-4'), 3.71 (dt, *J* = 29.8, 6.9 Hz, 2H, H_2-1), 3.52 – 3.62 (m, 6H, H_2-6, H_2-6', H-2, H-2'). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.2 – 137.6 (7 x C_q Bn), 129.1 – 125.4 (CH_{Ar} Bn), 99.2 (C-1'), 82.0 (C-3), 79.9 (C-3'), 79.7 (C-4'), 79.4 (C-2), 78.8 (C-4), 77.8 (C-2'), 75.7 – 72.8 (7 x CH_2 Bn), 71.8 (C-3'), 71.6 (C-6), 71.2 (C-5), 68.3 (C-6'), 61.6 (C-1). IR/cm^{-1}: 3420, 3063, 3030, 2862, 1454, 1207, 1086, 1070, 1028. $[\alpha]^{20}_D$ = +38.1 (c = 1.03, $CHCl_3$). HRMS: found 997.44972 $[C_{61}H_{66}O_{11}+Na]^+$, calculated for $[C_{61}H_{66}O_{11}+Na]^+$ 997.44973.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1-deoxynojirimycin (48):



48 was synthesised from **47** (1.0 g, 1.02 mmo) according to the procedure described for the preparation for compound **23**, to gain **48** (0.43 g, 0.45 mmol, 44% yield) as a light yellow oil. R_F = 0.38 (1:1 PE, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.26 (m, 35H, H_{Ar} Bn), 5.94 (d, *J* = 3.6 Hz, 1H, H-1'), 5.30 – 4.46 (m, 14H, 7 x CH_2 Bn), 4.11 (dd, *J* = 9.8, 8.5 Hz, 1H, H-3'), 3.98 (dd, *J* = 9.6, 8.7 Hz, 1H, H-4), 3.93 – 3.87 (m, 3H, H-5', H-6a, H-3), 3.84 (dd, *J* = 8.7, 1.3 Hz, 1H, H-4'), 3.81 (dd, *J* = 8.7, 5.6 Hz, 1H, H-6b), 3.73 (dd, *J* = 10.6, 2.8 Hz, 1H, H-6a'), 3.72 (td, *J* = 5.3, 2.2 Hz, 1H, H-2), 3.67 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2'), 3.61 (dd, *J* = 10.4, 1.3 Hz, 1H, H-6b'), 3.42 (dd, *J* = 12.3, 5.1 Hz, 1H, H-1a), 3.03 (ddd, *J* = 9.0, 5.7, 2.8, 1H, H-5), 2.70 (dd, *J* = 12.3, 10.6 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 – 137.9 (7 x C_q Bn), 128.3 – 126.5 (CH_{Ar} Bn), 96.6 (C-1'), 87.0 (C-3), 82.0 (C-3'), 80.9 (C-2), 79.3 (C-2'), 77.7 (C-4'), 75.5, 74.9 (2 x CH_2 Bn), 74.2 (C-4), 73.8 – 72.5 (5 x CH_2 Bn), 71.0 (C-5'), 70.5 (C-6), 68.1 (C-6'), 59.0 (C-5), 47.8 (C-1). $[\alpha]^{20}_D$ = +26.0 (c = 0.7, $CHCl_3$). IR/cm^{-1}: 2918, 2866, 1454, 1362, 1740, 1090, 1072, 1047, 1026. HRMS: found 956.47361 $[C_{61}H_{66}NO_9+Na]^+$, calculated for $[C_{61}H_{66}NO_9+Na]^+$ 956.47321.

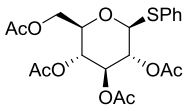
4-*O*-(β-D-Glucopyranosyl)-1-deoxynojirimycin (49):



49 was synthesised from **48** (1.00 g, 1.04 mmol) according to the procedure described for the preparation for compound **24**, to gain **49** (0.22 g, 0.67 mmol, 65% yield) as a light yellow oil. ^{1}H NMR (600 MHz, D_2O) δ 4.46 (d, *J* = 7.9 Hz, 1H, H-1'), 3.88 (dd, *J* = 12.3, 3.1 Hz, 1H, H-6a), 3.84 (dd, *J* =12.4, 2.2 Hz, 1H, H-6'a), 3.66 (dd, *J* = 12.4, 5.7 Hz, 1H, H-6'b), 3.66 – 3.62 (m, 1H, H-2), 3.62 (dd, *J* = 10.4, 8.9 Hz, H-5'), 3.49 (t, *J* = 9.1 Hz, 1H, H-3), 3.42 (t, *J* = 9.5 Hz, 1H, H-3'), 3.42 – 3.39 (m, 1H, H-5), 3.35 (dd, *J* = 9.8, 9.1 Hz, H-4'), 3.26 (dd, *J* = 12.7, 5.0 Hz, H-1a), 3.26 (dd, *J* = 9.4, 7.9 Hz, H-2'), 3.02 (ddd, *J* = 10.3, 5.0, 2.9 Hz, 1H, H-5), 2.70 (dd, *J* = 12.5, 11.2 Hz, 1H, H-1b). ^{13}C NMR (150 MHz, D_2O) δ 102.6 (C-1), 78.5 (C-4), 76.0 (C-5'), 75.6 (C-3'), 75.5 (C-3), 73.2 (C-2'), 69.4 (C-4'), 68.4 (C-2), 60.5 (C-6'), 59.2 (C-5), 58.4 (C-6), 46.6 (C-1). $[\alpha]^{20}_D$ = +25.3 (c = 1.0, MeOH). IR/cm^{-1}: 3302, 2966, 1636, 1558, 1203, 1161, 1022. HRMS: found 326.14464 $[C_{12}H_{23}NO_9+H]^+$, calculated for $[C_{12}H_{23}NO_9+H]^+$ 326.14456.

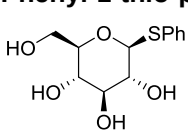
Synthesis of 2-*O*-(α-D-galactopyranpsyl-)-1-deoxynojirimycin (69)

Phenyl-1-thio-2,3,4,6-tetra-(*O*-acetyl)-β-D-glucopyranoside (51):



β-D-Glucose penta-acetate (0.996 g, 2.56 mmol) and PhSH (0.4 mL, 4 mmol) were dissolved in DCM (20 mL). The mixture was cooled to 0 °C and $BF_3{\cdot}Et_2O$ (0.46 mL, 3.7 mmol) was added dropwise. After 5 hours, TLC analysis showed complete consumption of the starting compound. The mixture was washed with sat. aq. $NaHCO_3$, organic layer was dried (Na_2SO_4), filtrated and concentrated. The crude product was purified with silica gel column chromatography to gain **51** as white crystal (1.02 g, 2.33 mmol, yield 91%). R_F = 0.7 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H, H_{Ar} SPh), 7.36 – 7.32 (m, 3H, H_{Ar} SPh), 5.24 (t, *J* = 9.3 Hz, 1H, H-3), 5.06 (t, *J* = 9.8 Hz, 1H, H-4), 4.99 (dd, *J* = 10.1, 9.2 Hz, 1H, H-2), 4.73 (d, *J* = 10.1 Hz, 1H, H-1), 4.24 (dd, *J* = 12.3, 5.0 Hz, 1H, H-6a), 4.20 (dd, *J* = 12.3, 2.7 Hz, 1H, H-6b), 3.75 (ddd, *J* = 10.1, 5.0, 2.7 Hz, 1H, H-5), 2.11 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.01 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.2, 169.4, 169.3 (4 x C=O), 131.6 (C_q SPh), 128.9 – 128.4 (C_{Ar} SPh), 85.7 (C-1), 75.8 (C-5), 74.0 (C-3), 69.9 (C-2), 68.2 (C-4), 62.1 (C-6), 20.7 – 20.6 (4 x CH_3).

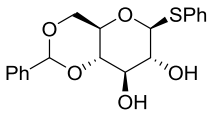
Phenyl-1-thio-β-D-glucopyranoside (52):



NaOMe (0.276 g, 5.12 mmol) was added to a solution of **51** (2.56 mmol) in MeOH (20 mL). After 24 hours, TLC analysis showed complete consumption of **51**. The solution was neutralized with amberlite H^+ resin, filtrated and

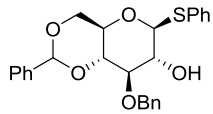
concentrated. The crude product was used for the next reaction step without further purification. R_F = 0.6 (5:1, EtOAc:MeOH). ^{1}H NMR (400 MHz, MeOD) δ 7.60 – 7.57 (m, 2H, H_{Ar} SPh), 7.35 – 7.26 (m, 3H, H_{Ar} SPh), 4.63 (d, *J* = 9.6 Hz, 1H, H-1), 3.91 (dd, *J* = 12.4, 1.6 Hz, 1H, H-6a), 3.71 (dd, *J* = 12.0, 5.6, 1H, H-6b), 3.43 (t, *J* = 8.8, 1H, H-4), 3.37 – 3.29 (m, 2H, H-3, H-5), 3.26 (dd, *J* = 9.6, 8.8, 1H, H-2). ^{13}C NMR (100 MHz, MeOD) δ 133.8 (C_q SPh), 131.3, 128.5, 127.0 (C_{Ar} SPh), 88.0 (C-1), 80.7 (C-3), 78.3 (C-4), 72.4 (C-2), 70.0 (C-5), 61.5 (C-6).

Phenyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (53):



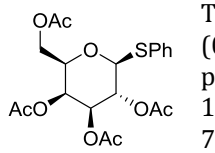
$PhCH(OMe)_2$ (5.7 mL, 38 mmol) was added to the solution of **52** (8.65 g, 31.6 mmol) in DMF (20 mL). *p*-TsOH was added to adjust the pH to 4. The mixture was heated to 60 °C and the pressure was reduced to 20 mbar. After 4.5 hours, TLC analysis showed complete consumption of **52**. The mixture was neutralized with TEA, diluted with EtOAc, washed successively with distilled water and brine, dried (Na_2SO_4), filtered, concentrated to get light yellow oil as crude product. The crude product was recrystallized from warm ethanol to get pure **53** as a white solid (19 mmol, yield 59% over two steps). R_F = 0.67 (2:1, EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H, H_{Ar} Ph), 7.59 – 7.57 (m, 3H, H_{Ar} Ph), 7.41 – 7.37 (m, 5H, H_{Ar} Ph), 5.57 (s, 1H, CH-benzylidene), 4.69 (d, *J* = 9.6 Hz, 1H, H-1), 4.44 (dd, *J* = 10.4, 4.4 Hz, 1H, H-6a) 3.91 (t, *J* = 8.8 Hz, 1H, H-3) 3.85 (dd, *J* = 7.2 Hz, 3.2 Hz, 1H, H-6b), 3.51 – 3.55 (m, 2H, H-4, H-5), 3.53 (dd, *J* = 11.8, 8.4 Hz, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.2 (C_q Ph), 133.1 – 126.3 (C_{Ar} Ph), 102.0 (C-7), 88.7 (C-1), 80.2 (C-4), 74.6 (C-3), 72.6 (C-2), 70.6 (C-5), 68.6 (C-6).

Phenyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (54):



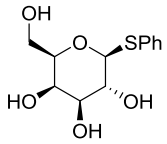
Bu_2SnO (0.35 g, 1.40 mmol) was added to a solution of **53** (0.48 g, 1.33 mmol) in toluene (17 mL), the reaction mixture was stirred overnight at 115 °C. Then toluene was evaporated, the residue was dissolved in DMF (10 mL), and CsF (0.31 g, 2.04 mmol), BnBr (0.3 mL, 2.5 mmol) was added. The reaction mixture was stirred at 115 °C for 12 hours. After TLC analysis showed complete consumption of **53**, the reaction mixture was diluted with ethyl acetate, washed successively with $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), concentrated and the residue was purified with a short column (8:1, PE:EtOAc) to gain **54** (0.44 g, yield 73.3%) as light yellow crystal. R_F = 0.66 (4:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (s, 1H, CH-benzylidene), 4.99 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.83 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.67 (d, *J* = 9.7 Hz, 1H, H-1), 4.42 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6a), 3.83 (t, *J* = 10.3 Hz, 1H, H-6b), 3.76-3.63 (m, 2H, H-3, H-4), 3.58 – 3.53 (m, 2H, H-2, H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.2 (C_q Ph), 133.2 – 126.0 (C_{Ar} Ph), 101.3 (CH-benzylidene), 88.5 (C-1), 81.7 (C-3), 81.1 (C-4), 74.8 (CH_2 Bn), 72.3 (C-2), 70.7 (C-5), 68.6 (C-6).

Phenyl-1-thio-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (56):



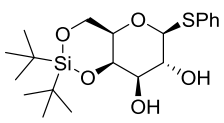
The title compound was synthesized from **55** (1.00 g, 2.56 mmol), thiophenol (0.4 mL, 3.91 mmol) and $BF_3{\cdot}Et_2O$ (0.46 mL, 3.72 mmol) according to the procedure described for the preparation of **51** to gain **56** (1.2 g, 2.5 mmol, 100%) as white crystal. R_F = 0.68 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.52 (m, 2H, H_{Ar}), 7.34 – 7.32 (m, 3H, H_{Ar}), 5.44 (d, *J* = 3.2, 1H, H-1), 5.28 (t, *J* = 10 Hz, 1H, H-2), 5.08 (dd, *J* = 10, 3.6 Hz, 1H, H-3), 4.75 (d, *J* = 10.0 Hz, 1H, H-4), 4.23 (dd, *J* = 11.2, 7.2 Hz, 1H, H-6a), 4.15 (dd, *J* = 11.6, 6 Hz, 1H, H-6b), 3.98 (t, *J* = 6.4 Hz, 1H, H-5), 2.14 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 – 169.5 (4 x C=O), 132.6 (C_{Ar}), 132.5 (C_q Ph), 129.0, 128.2 (C_{Ar}), 86.6 (C-1), 74.4 (C-5), 72.0 (C-3), 67.3 (C-2), 67.2 (C-4), 61.7 (C-6), 20.9 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 20.7 (CH_3).

Phenyl-1-thio-β-D-galactopyranoside (57):



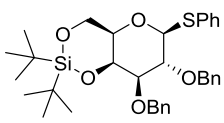
The title compound was synthesized from **57** (59.00 g, 133.95 mmol), thiophenol (0.4 mL, 3.91 mmol) and $BF_3{\cdot}Et_2O$ (0.46 mL, 3.72 mmol) according to the procedure described for the preparation of **52** to gain **57** as crude product and used in next step without further purification. R_F = 0.5 (5:1, EtOAc:MeOH). ^{1}H NMR (400 MHz, MeOD) δ 7.56 – 7.54 (m, 2H, H_{Ar} SPh), 7.31 – 7.21 (m, 3H, H_{Ar} SPh), 4.59 (d, *J* = 8.0 Hz, 1H, H-1), 3.90 (d, *J* = 4.0 Hz, 1H, H=4), 3.76 (dd, *J* = 12.0, 8.0 Hz, 1H, H-6a), 3.71 (dd, *J* = 12.0, 4 Hz, 1H, H-6b), 3.59 – 3.55 (m, 2H, H-5, H-2), 3.50 (dd, *J* = 12.0, 4 Hz, 1H, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1 (C_q SPh), 132.1 – 128.0 (C_{Ar} SPh), 90.3 (C-1), 80.6 (C-3), 76.3 (C-4), 71.0 (C-2), 70.4 (C-5), 62.6 (C-6).

Phenyl-4,6-*O*-di-*tert*-butylsilylene-1-thio-β-D-galactopyranoside (58):



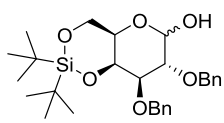
57 (3.12 g, 11.5 mmol) was co-evaporated with DMF. The mixture was dissolved in pyridine (20 mL). The solution was cooled to -20 °C and *t*BuSi(OTf)$_2$ (3.5 mL, 9.9 mmol) was added. After 2 hours, TLC analysis showed complete consumption of **57**. Methanol was added to quench the reaction. The volatiles were evaporated and the residue was diluted with EtOAc, washed with HCl (1M) and sat. aq. $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtrated and concentrated. The residue was purified with silica gel column chromatography (1:4 → 1:3, EtOAc:PE) to gain **52** (2.49 g, 6.04 mmol, yield 53%) as light yellow oil. R_F = 0.34 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H, H_{Ar} SPh), 7.39 – 7.30 (m, 3H, H_{Ar} SPh), 4.58 (d, *J* = 9.8 Hz, 1H, H-1), 4.46 (dd, *J* = 3.5, 1.1 Hz, 1H, H-4), 4.29 (dd, *J* = 2.0, 1.1 Hz, 2H, H_2-6), 3.77 (dd, *J* = 9.8, 8.9 Hz, 1H, H-2), 3.56 (dd, *J* = 8.9, 3.5 Hz, 1H, H-3), 3.50 (td, *J* = 2.0, 1.1 Hz, 1H, H-5), 1.08 (s, 9H, 3 x CH_3, *tert*-Bu), 1.06 (s, 9H, 3 x CH_3, *tert*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1 (C_q), 132.6 – 127.9 (C_{Ar} SPh), 89.1 (C-1), 75.2 (C-5), 75.1 (C-3), 72.5 (C-4), 70.7 (C-2), 67.1 (C-6), 27.6 – 20.7 (6 x CH_3, *tert*-Bu).

Phenyl-2,3-di-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylene-1-thio-β-D-galactopyranoside (59):



58 (15.74 g, 38.15 mmol) was dissolved in DMF (20 mL). BnBr (9 mL, 76 mmol) and TBAI (16.75 g, 68.68 mmol) were added. The mixture was cooled to 0 °C and NaH (8.2 g, 0.21 mmol) was added in small potions. After an overnight reaction, TLC analysis showed complete consumption of **58**. The mixture was quenched by the addition of water, diluted with EtOAc and washed with brine. The organic layer was dried (Na_2SO_4), filtrated and concentrated. The residue was purified with silica gel column chromatography (20:1 → 10:1, PE:EtOAc) to gain **59** (12.66 g, 21.35 mmol, yield 56%) as thick oil. R_F = 0.4 (5:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.27 (m, 12H, H_{Ar} Bn/SPh), 4.94 (s, 2H, CH_2 Bn), 4.80 (q, *J* = 12 Hz, 2H, CH_2 Bn), 4.71 (d, *J* = 9.6 Hz, 1H, H-1), 4.53 (d, *J* = 2.8 Hz, 1H, H-4), 4.24 (m, 2H, H_2-6), 3.89 (t, *J* = 9.6 Hz, 1H, H-2), 3.52 (dd, *J* = 9.2, 3.2 Hz, 1H, H-3), 3.32 (s, 1H, H-5), 1.17 (s, 9H, 3 x CH_3, *tert*-Bu), 1.12 (s, 9H, 3 x CH_3, *tert*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.9 (C_q Bn), 132.1 – 127.3 (CH_{Ar} Bn/SPh), 88.7 (C-1), 82.8 (C-3), 77.0 (C-2), 76.0 (CH_2 Bn), 74.8 (C-5), 71.1 (CH_2 Bn), 70.0 (C-4), 67.4 (C-6), 27.7, 27.7 (CH_3, *tert*-Bu), 23.5 (C_q, *tert*-Bu), 20.8 (C_q, *tert*-Bu).

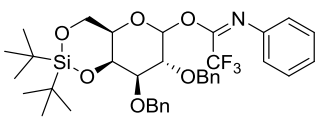
2,3-Di-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylene-D-galactopyranoside (60):



59 (0.61 g, 1.0 mmol) was co-evaporated with toluene (3 x) and dissolved in DCM (50 mL). The solution was cooled to 0 °C. *N*-Iodosuccinimide (0.227 g, 1.03 mmol) and TFA (77 µL, 1.0 mmol) were added to the solution. After 1 hour, TLC analysis showed complete consumption of **59**. The reaction was quenched by adding TEA, and sat. aq. $Na_2S_2O_3$ was added to the mixture. The mixture was extracted with EtOAc, and the organic layer was dried (Na_2SO_4), filtrated and concentrated. The resulting residue was purified with silica gel column chromatography (10:1

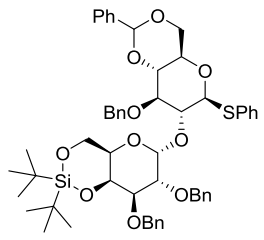
→ 2:1, PE:EtOAc) to gain **60** (0.451 g, 0.903 mmol, yield 88%). R_F = 0.28 (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 10H, H_{Ar} Bn), 5.23 (d, *J* = 3.6 Hz, 1H, H-1), 4.92 (d, *J* = 11.6 Hz, 2H, CH_2 Bn), 4.81 – 4.72 (m, 2H, CH_2 Bn), 4.54 (d, *J* = 3.0 Hz, 1H, H-4), 4.21 – 4.12 (m, 2H, H_2-6), 4.02 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 3.87 (d, *J* = 3.2 Hz, 1H, H-5), 3.84 (d, *J* = 2.8 Hz, 1H, H-3), 1.12 (s, 9H, 3 x CH_3, *tert*-Bu), 1.08 (s, 9H, 3 x CH_3, *tert*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.3 (C_q Bn), 128.4 – 127.6 (CH_{Ar} Bn), 92.1 (C-1), 77.5 (C-3), 74.8 (C-2), 74.8 (CH_2 Bn), 71.0 (C-4), 71.0 (CH_2 Bn), 67.4 (C-6), 67.3 (C-5), 27.7 (CH_3), 27.7 (CH_3), 27.6, 27.4 (CH_3, *tert*-Bu), 23.5, 20.7 (C_q, *tert*-Bu).

2,3-Di-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilanediyl-D-galactopyranoside-*N*-phenyl-2,2,2-trifluoroacetimidate (61):



Cs_2CO_3 (0.28 g, 0.85 mmol) and trifluoro-phenylacetimidoyl chloride (0.20 g, 0.96 mmol) was added to a solution of **60** (0.27 g, 0.54 mmol) in acetone (3 mL). The reaction mixture was kept at 0 °C under argon atmosphere. After 3 hours, the reaction mixture was filtrated through a pad of Celite. The filtrate was concentrated and purified on a short column (20:1 → 2:1, PE:EtOAc) to get **61** (0.22 g, 0.26 mmol, yield 65%) as anomeric mixture at ratio 1:1. R_F = 0.56, 0.38 (10:1, PE:EtOAc). For the upper spot on TLC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 6.78 (m, 15H, H_{Ar} Bn/Ph), 6.55 (br s, 1H, H-1), 4.89 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.85 – 4.72 (m, 3H, 3 x CH*H* Bn), 4.62 (br s, 1H, H-4), 4.33 – 4.18 (m, 3H, H_2-6, H-2), 3.91 (d, *J* = 10.1 Hz, 1H, H-3), 3.81 (br s, 1H, H-5), 1.10 (s, 9H, 3 x CH_3, *tert*-Bu), 1.02 (s, 9H, 3 x CH_3, *tert*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C=N), 143.8, 138.6, 138.2 (C_q Bn), 129.1 – 120.6 (CH_{Ar} Bn), 100.0 (CF_3), 94.8 (H-1), 77.3 (C-3), 73.7 (CH_2 Bn), 73.6 (C-2), 71.1 (CH_2 Bn), 70.7 (C-4), 70.0 (C-5), 66.8 (C-6), 27.6, 27.2 (CH_3, *tert*-Bu), 23.5, 20.7 (C_q, *tert*-Bu).

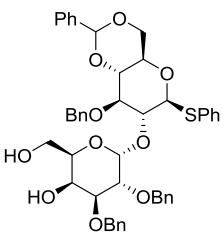
3-Benzyl-4,6-*O*-benzylidene-2-*O*-(2,3-di-benzyl-4,6-*O*-di-*tert*-butylsilyl-galactopyranpsyl)-1-thio-D-glucopyranose (62):



54 (0.405 g, 0.899 mmol) and **61** (1.201 g, 1.788 mmol) were co-evaporated with toluene (3 x). The residue was dissolved in dried DCM (4 mL) and cooled to 0 °C, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.045 mL, 0.25 mmol). After an overnight reaction, TLC analysis showed complete consumption of **61**. The reaction was quenched by the addition of TEA and concentrated. The resulting residue was purified with silica gel column chromatography (40:1 → 10:1, PE:EtOAc). Yield 69% (0.56 g, 0. 61 mmol). R_F = 0.15 (10:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.04 (m, 25H, H_{Ar}), 5.89 (d, *J* = 4 Hz, 1H, H-1'), 5.65 (s, 1H, CH-benzylidene), 5.09 (d, *J* = 10 Hz, 1H, CH*H Bn*), 4.97 (d, *J* = 9.2 Hz, 1H, H-1), 4.89 (s, 2H, CH_2 Bn), 4.81 (q, *J* = 12 Hz, 2H, CH_2 Bn), 4.43 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6a), 4.33 (d, *J* = 10.4 Hz, 1H, CH*H* Bn), 4.07 (dd, *J* = 10.0, 3.6 Hz, 1H, H-2'), 4.02 (d, *J* = 8.0 Hz, 1H, H-4'), 3.89 – 3.72 (m, 6H, H-3, H-2, H-5', H-6b, H-3', H-4), 3.56 (dd, *J* = 12.8, 1.6 Hz, 1H, H-6'a), 3.60 – 3.53 (m, 1H, H-5), 3.02 (dd, *J* = 12.6, 2.2 Hz, 1H, H-6'b), 1.02 (s, 9H, CH_3, *tert*-Bu), 0.99 (s, 9H, CH_3, *tert*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 – 126.0 (C_{Ar}), 101.1 (CH-benzylidene), 96.2 (C-1'), 87.6 (C-1'), 82.2 (C-3), 81.0 (C-4), 77.0 (C-3'), 76.2 (CH_2 Bn), 74.2 (C-2'), 73.7 (CH_2 Bn), 72.7 (C-2), 71.2 (CH_2 Bn), 71.0 (C-4'), 70.0 (C-5), 68.7 (C-6), 66.9 (C-3'), 66.5 (C-6'), 27.7, 27.3 (CH_3, *tert*-Bu), 23.3 (C_q, *tert*-Bu), 20.6 (C_q, *tert*-Bu).

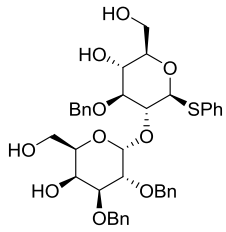
Phenyl-1-thio-2-*O*-(2,3-di-*O*-benzyl-α- galactopyranosyl)-3-benzyl-4,6-*O*-benzylidene-D-glucopyranose (63):

TBAF (1M in THF, 1.2 mL, 1.2 mmol) was added dropwise to a solution of **62** (0.16 g, 0.17 mmol) in THF (2 mL) at 0 °C, and the yellow solution was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified with silica gel column



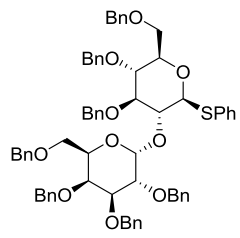
chromatography (5:2 → 1:1, PE:EtOAc) to get pure **63** (0.11 g, 0.14 mmol, yield 82%). R_F = 0.17 (5:2, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.17 (m, 25H, H_{Ar}), 6.01 (d, *J* = 3.8 Hz, 1H, H-1'), 5.63 (s, 1H, CH-benzylidene), 5.10 (d, *J* = 10.7 Hz, 1H, CH*H* Bn), 4.96 (d, *J* = 9.3 Hz, 1H, H-1), 4.87 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.84 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.77 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.71 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 10.7 Hz, 1H, CH*H* Bn), 4.41 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6a), 4.06 (t, *J* = 4.8 Hz, 1H, H-5'), 3.96 – 3.90 (m, 3H, H-2, H-2', H-3), 3.84 (d, *J* = 10.2 Hz, 1H, H-6b), 3.81 – 3.78 (m, 1H, H-4), 3.75 (dd, *J* = 10.0, 3.2 Hz, 1H, H-3'), 3.59 (dd, *J* = 3.2, 1.5 Hz, 1H, H-4'), 3.55 (dt, *J* = 9.8, 4.8 Hz, 1H, H-5), 3.30 (dd, *J* = 11.8, 5.4 Hz, 1H, H-6'a), 3.23 (dd, *J* = 11.8, 4.3 Hz, 1H, H-6'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 – 125.9 (C_{Ar}), 101.1 (CH-benzylidene), 95.7 (C-1'), 87.5 (C-1), 82.0 (C-4), 81.9 (C-3) 76.7 (C-3'), 76.0 (CH_2 Bn), 75.4 (C-2'), 73.3 (CH_2 Bn), 73.2 (C-2), 72.8 (CH_2 Bn), 70.0 (C-5), 69.9 (C-4'),68.6 (C-6), 68.4 (C-5'), 63.1 (C-6'). $[\alpha]^{20}_D$ = +22.1 (c = 0.85, $CHCl_3$). HRMS: found 815.28588 $[C_{46}H_{48}O_{10}S+Na]^+$, calculated for $[C_{46}H_{48}O_{10}S+Na]^+$ 815.28604.

Phenyl-1-thio-2-*O*-(2,3-di-*O*-benzyl-α-galactopyranosyl)-3-benzyl-D-glucopyranose (64):



p-Toluenesulfonic acid monohydrate (0.065 g, 0.34 mmol) was added to a solution of **63** (0.10 g, 0.13 mmol) in methanol and DCM (10 mL, 1:1, v/v), and the reaction mixture was kept stirred at room temperature overnight. After quenching by the addition of TEA, the reaction mixture was concentrated and purified with silica gel column chromatography (1:1, pentane: EtOAc) to give **64** (0.08 g, yield 90%). R_F = 0.1 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.16 (m, 15H, H_{Ar}), 5.97 (d, *J* = 3.7 Hz, 1H, H-1'), 5.06 (d, *J* = 11.2 Hz, 1H, CH*H* Bn), 4.91 (d, *J* = 9.7 Hz, 1H, H-1), 4.87 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.82 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.76 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.71 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.58 (d, *J* = 11.2 Hz, 1H, CH*H* Bn), 4.05 (td, *J* = 5.2, 4.7, 2.3 Hz, 1H, H-5'), 3.93 (dd, *J* = 10.1, 3.9 Hz, 1H, H-2'), 3.90 – 3.79 (m, 4H, H-6a, H-2, H-6b, H-3), 3.76 (dd, *J* = 10.0, 3.2 Hz, 1H, H-3'), 3.66 (t, *J* = 9.0 Hz, 1H, H-4), 3.54 (d, *J* = 2.9 Hz, 1H, H-4'), 3.42 – 3.34 (m, 2H, H-6'a, H-5), 3.26 (dd, *J* = 11.8, 4.0 Hz, 1H, H-6'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 – 126.3 (C_{Ar}), 95.5 (C-1'), 87.4 (C-1), 85.4 (C-4), 79.3 (C-5), 76.6 (C-3'), 76.2 (CH_2 Bn), 75.4 (C-2'), 73.2 (CH_2 Bn), 73.1 (C-2), 72.7 (CH_2 Bn), 71.1 (C-3), 69.1 (C-4'), 68.6 (C-5'), 62.9 (C-6'), 62.0 (C-6). $[\alpha]^{20}_D$ = +16.3 (c = 2.45, $CHCl_3$). HRMS: found 727.25414 $[C_{39}H_{44}O_{10}+Na]^+$, calculated for $[C_{39}H_{44}O_{10}+Na]^+$ 727.25474.

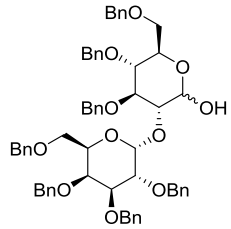
Phenyl-1-thio-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-galactopyranosyl)-3,4,6-tri-benzyl-D-glucopyranose (65):



NaH (60% on mineral oil, 48.8 mg, 1.22mmol) was added to a solution of **64** (0.08 g, 0.11 mmol) in DMF (1 mL) at 0 °C under argon atmosphere, the suspension was stirred at 0 °C for 1 hour. Then BnBr (0.067 mL, 0.56 mmol) was added. The reaction mixture was kept stirred at room temperature overnight. After quenched by the addition of water, the reaction mixture was extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, concentrated and purified with silica gel column chromatography (20:1, pentane:EtOAc) to get pure **65** (0.11g, 0.10 mmol, yield 92%). R_F = 0.62 (5:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.09 (m, 40H, H_{Ar}), 6.01 (d, *J* = 3.7 Hz, 1H, H-1'), 4.98 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.92 – 4.53 (m, 10H, 5 x CH_2 Bn), 4.49 (d, *J* = 11.4 Hz, 1H, CH*H* Bn), 4.33 (t, *J* = 6.5 Hz, 1H, H-5'), 4.30 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.22 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.12 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2'), 3.97 (t, *J* = 9.1 Hz, 1H, H-2), 3.89 (dd, *J* = 10.2, 2.7 Hz, 1H, H-3'), 3.81 – 3.72 (m, 3H, H_2-6, H-4), 3.65 (t, *J* = 9.3 Hz, 1H, H-3), 3.60 (dd, *J* = 2.9, 1.3 Hz, 1H, H-4'), 3.55 (ddd, *J* = 9.8, 4.5, 2.1 Hz, 1H, H-5), 3.44 (dd, *J* =

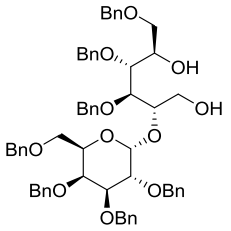
9.5, 6.4 Hz, 1H, H-6'a), 3.28 – 3.23 (m, 1H, H-6'b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9 – 127.1 (C_{Ar}), 95.6 (C-1'), 87.1 (C-1), 85.2 (C-4), 79.0 (C-5), 78.5 (C-3), 78.3 (C-3'), 76.3 (C-2'), 75.5 (CH_2 Bn), 75.2 (C-4'), 74.9 (CH_2 Bn), 74.7 (CH_2 Bn), 73.5 (CH_2 Bn), 73.4 (C-2), 73.1 (CH_2 Bn), 73.0 (CH_2 Bn), 69.3 (C-5'), 69.1 (C-6'), 68.9 (C-6).

2-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-galactopyranpsyl)-3,4,6-tri-*O*-benzyl-D-glucopyranose (66):



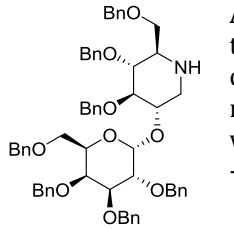
NIS (0.13 g, 0.53 mmol) and TFA (35 µL) was added to a solution of **65** (0.44 g, 0.41 mmol) in dried DCM (5 mL) at 0 °C under argon atmosphere. The reaction was stirred at room temperature for 2 hours. Piperidine was added to quench the reaction at 0 °C, after which sat. aq. $Na_2S_2O_3$ solution was added. The reaction mixture was extracted with EtOAc, washed with HCl solution (1M) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified with silica gel column chromatography (4:1 → 2:1, PE:EtOAc) to gain pure **66** (0.28 g, 0.29 mmol, yield 71%) as a mixture of two isomers (2:5). R_F = 0.3 (4:1, PE:EtOAc). For the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, *J* = 3.4 Hz, 1H, H-1'), 4.99 – 4.50 (m, 13H, 6 x CH_2 Bn, H-1), 4.41 – 4.28 (m, 2H, CH_2 Bn), 4.15 (d, *J* = 7.2 Hz, 1H, H-5), 4.12 – 4.05 (m, 2H, H-5', H-2), 4.00 – 3.89 (m, 3H, H-4, H-4', H-3'), 3.85 (dd, *J* = 9.0, 3.4 Hz, 1H, H-2'), 3.83 – 3.70 (m, 3H, H_2-6', H-3), 3.49 – 3.45 (m, 2H, H_2-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 – 127.5 (C_{Ar}), 96.5 (C-1), 90.3 (C-1'), 80.3 (C-4), 79.0 (C-4'), 77.5 (C-3), 77.3 (CH_2 Bn), 75.4 (C-2'), 75.3 (CH_2 Bn), 74.8 (CH_2 Bn), 74.5 (C-2), 74.3, 73.6, 73.2, 72.5 (4 x CH_2 Bn), 70.9 (C-5'), 69.7 (C-5), 68.6 (C-6'), 68.5 (C-6).

2-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-galactopyranosyl)-3,4,6-tri-*O*-benzyl-D-glucitol (67):



$LiAlH_4$ (0.5 mL, 2.4 M in THF, 1.2 mmol) was added dropwise into a solution of **66** (0.25 g, 0.26 mmol) in THF (3 mL) at 0 °C under argon atmosphere. After stirred overnight, the reaction mixture was slowly quenched by the addition of methanol, after which HCl (1M, 3 mL) was added. Then the mixture was diluted with ethyl acetate and washed with brine, the water layer was reextracted with EtOAc. The organic layers were combined, dried (Na_2SO_4), filtered and concentrated. The crude product was purified with silica gel column chromatography (2:1 → 1:1, PE:EtOAc) to gain **67** (0.22 g, 0.23 mmol, yield 88%). R_F = 0.58 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, *J* = 3.5 Hz, 1H, H-1'), 4.96 – 4.86 (m, 2H, CH_2 Bn), 4.79 – 4.51 (m, 6H, 3 x CH_2 Bn), 4.45 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.35 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.14 – 4.04 (m, 2H, H-2, H-5'), 4.11 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2'), 4.00 – 3.98 (m, 1H, H-5), 3.98 (dd, *J* = 10.1, 2.6 Hz, 1H, H-3') 3.92 – 3.82 (m, 3H, H-3, H-4', H-4), 3.81 – 3.76 (m, 1H, H-6a), 3.76 – 3.71 (m, 2H, H_2-6'), 3.69 – 3.64 (m, 1H, H-6b), 3.52 (dd, *J* = 9.3, 6.7 Hz, 1H, H-1a), 3.38 (dd, *J* = 9.4, 5.8 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 – 127.5 (C_{Ar}), 99.9 (C-1'), 81.8 (C-5), 79.3 (C-3'), 79.2 (C-4'), 79.2 (C-3), 76.2 (C-2'), 74.7 (C-4), 74.6 – 72.6 (7 x CH_2 Bn), 71.2 (C-6'), 70.7 (C-5'), 70.4 (C-2), 69.4 (C-1), 62.5 (C-6). $[\alpha]^{20}_D$ = +39.1 (c = 1.17, $CHCl_3$). HRMS: found 997.44983 $[C_{61}H_{66}O_{11}+Na]^+$, calculated for $[C_{61}H_{66}O_{11}+Na]^+$ 997.44973.

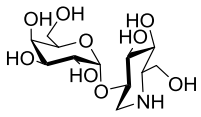
2-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-galactopyranpsyl)-3,4,6-tri-*O*-benzyl-1-deoxynojirimycin (68):



A solution of $(COCl)_2$ (100 µL, 1.16 mmol) in dry DCM (1.5 mL) was cooled to -78 °C under argon atmosphere. DMSO (100 µL, 1.40 mmol) dissolved in dry DCM (1.5 mL) was added dropwise. After 40 minutes **67** (0.32 g, 0.33 mmol, which was co-evaporated with toluene 3 x), in dry DCM (7.5 mL), was added dropwise to the mixture. The reaction was stirred for 2 hours at -78 °C, after which Et_3N (0.51 mL, 3.65 mmol) was added dropwise. The

mixture was gradually warmed to -40 °C in more than 1 hour, after which it was poured into a cooled (0 °C) MeOH solution (60 mL) containing $NaCNBH_3$ (0.09 g, 1.44 mmol), $HCOONH_4$ (0.49 g, 7.76 mmol), and Na_2SO_4 (0.19 g, 1.34 mmol). The mixture was stirred overnight allowing the reaction to reach room temperature. TLC analysis showed the formation of the product (2:1, PE:EtOAc, R_F = 0.37). After filtration, the volatiles were evaporated, as the residue was dissolved in EtOAc (100 mL). The solution was washed with sat. aq. $NaHCO_3$ solution, dried (Na_2SO_4) filtered and concentrated. The residue was purified with silica gel column chromatography (5:1 → 2:3, PE:EtOAc) to give **62** in 24% yield (0.07 g, 0.073 mmol). R_F = 0.37 (2:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 – 4.80 (m, 7H, H-1', 3 x CH_2 Bn), 4.72 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.67 (d, *J* = 12.1 Hz, 1H, CH*H* Bn), 4.57 – 4.44 (m, 4H, 2 x CH_2 Bn), 4.31 (d, *J* = 6.2 Hz, 2H, CH_2 Bn), 4.20 (td, *J* = 6.5, 1.3 Hz, 1H, H-5'), 4.05 (dd, *J* = 10.1, 3.6 Hz, 1H, H-2'), 3.89 (dd, *J* = 10.1, 2.9 Hz, 1H, H-3'), 3.75 (dd, *J* = 9.2, 4.6 Hz, 1H, H-2), 3.72 – 3.69 (m, 2H, H-6a, H-4'), 3.65 – 3.59 (m, 1H, H-6b), 3.60 (t, *J* = 9.2 Hz, 1H, H-3), 3.52 (dd, *J* = 9.6, 6.4 Hz, 1H, H-6'a), 3.41 (t, *J* = 9.3 Hz, 1H, H-4), 3.32 (dd, *J* = 9.6, 6.6 Hz, 1H, H-6'b), 3.25 (dd, *J* = 12.5, 4.8 Hz, 1H, H-1a), 2.76 (ddd, *J* = 9.3, 5.0, 2.6 Hz, 1H, H-5), 2.56 (dd, *J* = 12.5, 10.4 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 – 127.5 (C_{Ar}), 94.5 (C-1'), 85.9 (C-3), 80.4 (C-4), 78.7 (C-3'), 76.5 (C-2'), 75.6 (CH_2 Bn), 75.2 (C-4'), 75.2 (CH_2 Bn), 74.8 (CH_2 Bn), 74.8 (C-2), 73.7 (CH_2 Bn), 73.5 – 72.9 (4 x CH_2 Bn), 69.8 (C-6), 68.9 (C-6'), 68.8 (C-5'), 59.7 (C-5), 46.5 (C-1). $[\alpha]^{20}_D$ = +76.9 (c = 0.32, $CHCl_3$). HRMS: found 956.47350 $[C_{61}H_{65}NO_9+H]^+$, calculated for $[C_{61}H_{65}NO_9+H]^+$ 956.47321.

2-*O*-(α-D-galactopyranpsyl-)-1-deoxynojirimycin (69):



62 (0.2 g, 0.21 mmol) was dissolved in ethanol (6 mL), pH of the solution was adjusted to 2 with 1M HCl. Pd/C (10%) was added, the mixture was shaken under H_2 atmosphere at 4 bar for 24 hours. The catalyst was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified on size exclusion column chromatography (eluent: NH_4Ac, 0.15 M, aq.) to get pure **69** (35 mg, 0.11 mmol, yield 52%). ^{1}H NMR (400 MHz, D_2O) δ 4.93 (d, *J* = 3.8 Hz, 1H, H-1'), 4.05 (t, *J* = 6.4 Hz, 1H, H-5'), 3.85 (d, *J* = 3.2 Hz, 1H, H-4'), 3.80 (dd, *J* = 12.8, 3.1 Hz, 1H, H-6a), 3.77 – 3.70 (m, 3H, H-6b, H-2, H-3'), 3.68 (dd, *J* = 10.5, 3.7 Hz, 1H, H-2'), 3.58 (d, *J* = 6.2 Hz, 2H, H-6'), 3.54 (dd, *J* = 12.6, 5.0 Hz, 1H, H-1a), 3.52 – 3.49 (m, 2H, H-3, H-4), 3.06 (ddt, *J* = 8.0, 5.4, 3.1 Hz, 1H, H-5), 2.84 (dd, *J* = 12.5, 11.5 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, D_2O) δ 100.0 (C-1'), 74.4 (C-3), 71.6 (C-3'), 70.9 (C-5'), 69.0 (C-2), 69.0 (C-4'), 67.8 (C-2'), 67.6 (C-4), 60.8 (C-6'), 59.8 (C-5), 57.6 (C-6), 43.2 (C-1). HRMS: found 364.10099 $[C_{12}H_{23}NO_9+K]^+$, calculated for $[C_{12}H_{23}NO_9+K]^+$ 364.10044.

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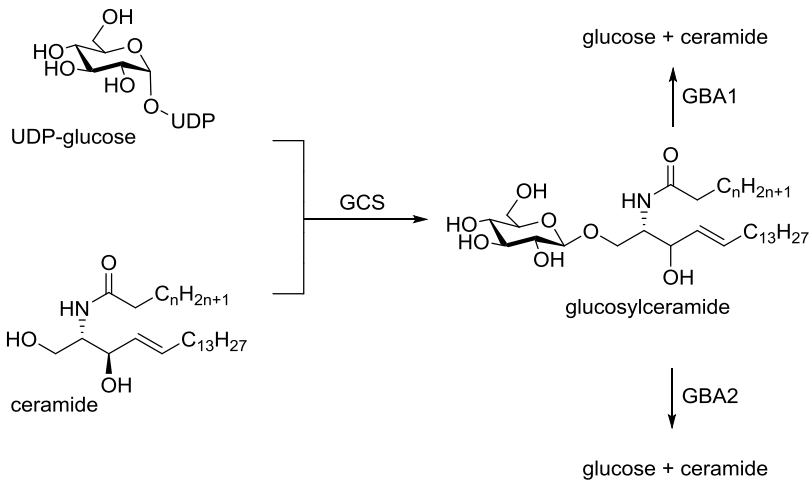
4 Discovery of *N*-alkyl Deoxynojirimycin Derivatives as Potential GBA2 Inhibitors

Introduction

GBA2 (EC3.2.1.45, GH116) is a membrane-bound, non-lysosomal retaining β-glucosidase. GBA2 was first described by Matern *et al*. who annotated the enzyme as a bile acid active glycosidase,[1] but is now widely known to partake in the degradation of glucosylceramide (GlcCer).[2] GBA2 is associated with a number of physiological and pathological processes, such as neuronal development, lysosomal storage diseases (LSD), tumorigenicity and inflammatory diseases.[3]

GlcCer is synthesized on the outer endoplasmic reticulum leaflet by glucosylceramide synthase (GCS) from UDP-glucose and ceramide (Figure 1), and degraded in lysosomes by lysosomal glucocerebrosidase (GBA1).[4] In Gaucher disease and Niemann-Pick type C disease (caused by genetic deficiency of GBA1 and acid sphingomyelinase, respectively), GlcCer accumulates in lysosomes, from where it spills over into the cytoplasm where it is degraded by GBA2. This degradation leads to an increase of ceramide concentration in the cytoplasm, which may be responsible for several symptoms observed in patients suffering from Gaucher and Niemann-Pick type C.[5] Mistry *et al*. reported[6] that genetic deletion of the GBA2 gene can relieve clinical symptoms in Gaucher diseased mice, which indicates that GBA2 is a potential target for Gaucher disease treatment. This finding is consistent with the hypothesis that compensatory GBA2 overexpression in Gaucher disease has deleterious effects.[7]

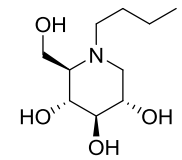
Figure 1*: Glucosylceramide metabolism*



Although GBA2 has been identified to be present in various tissues,[8] its expression and activity appears most abundant in the central nervous system.[9] This indicates that GBA2 may play a role in neuronal development. Relevant evidence to support this observation was shown by Martin *et al.* who demonstrated that the loss of GBA2 function is responsible for motor neuron defects in hereditary spastic paraplegia.[10] Also, mutations in the gene encoding for GBA2 were found in patients suffering from cerebella ataxia, spastic paraplegia, thin corpus callosum and cognitive impairment.[11] These findings underscore the potential correlation between GBA2 and neurodegenerative diseases. GBA2 activity has been connected with tumor biology as well. Inducibly overexpressed GBA2 leads to a decreased anchorage-independent human melanoma cell growth, and thus to the decrease of *in vivo* melanoma tumor growth.[12] In addition, GBA2 activity has also been associated with inflammatory responses. Mistry *et al*. reported that GBA2-deficient mice produce significantly lower amounts of several pro-

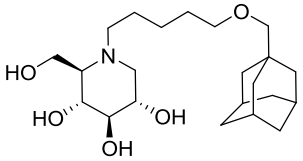
inflammatory cytokines, which indicates that GBA2 may be a relevant target for drugs aiming for reducing inflammation.[6] For all these reasons, the identification of inhibitors selective for GBA2 is a relevant research objective.

***Figure 2**: Structure and IC_{50} values of the lead compounds.*

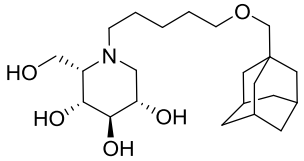


1, Zavesca

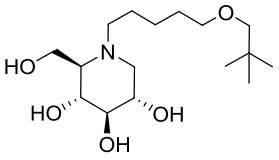
IC_{50} GCS 50 μM
IC_{50} GBA1 520 μM
IC_{50} GBA2 0.3 μM



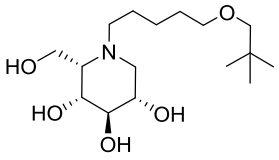
2, MZ-21 IC_{50} GCS 200 nM
IC_{50} GBA1 0.1 μM
IC_{50} GBA2 2 nM



3, MZ-31 IC_{50} GCS 100 nM
IC_{50} GBA1 30 μM
IC_{50} GBA2 1 nM



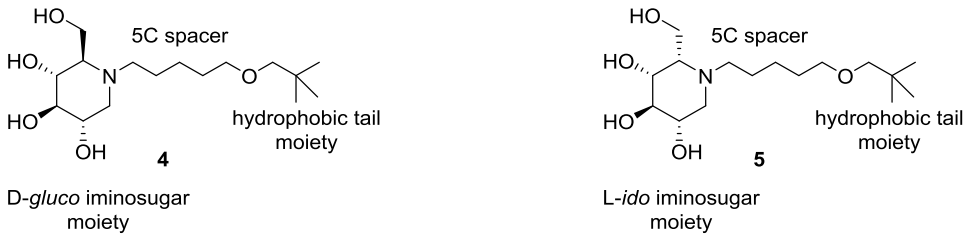
4 , DNJ-NEO IC_{50} GCS 5 μM
IC_{50} GBA1 6 μM
IC_{50} GBA2 5 nM



5, L-*ido* NEO IC_{50} GCS 1.6 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 nM

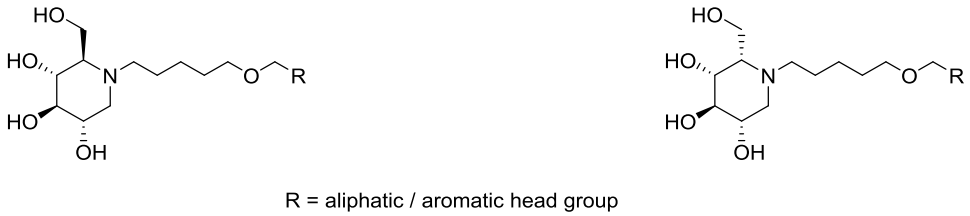
N-alkyl-deoxynojirimycin derivatives are potent GBA2 inhibitors that however display inhibitory activity against the other GlcCer-metabolizing enzymes, GCS and GBA1, as well (Figure 2). *N*-Butyl-deoxynojirimycin (*N*-butyl-DNJ, Zavesca, **1**), a moderately potent GCS inhibitor that at lower concentrations also blocks GBA2 activity, is in clinical use for the treatment of non-neuronopathic Gaucher patients. Inspired by the clinical success of *N*-butyl-DNJ (**1**), a large number of *N*-alkyl-DNJ derivatives have appeared in the literature and that vary in the nature of the *N*-alkyl group, in the configuration of the polyhydroxylated piperidine or a combination thereof.[13-15] Amongst these compounds, *N*-adamantanemethyloxypentyl-DNJ (**2**, MZ-21) and its L-*ido*-configured isoster (**3**, MZ-31) were identified as very potent GCS inhibitors (much more than the clinical compound, Zavesca **1**) that also strongly inhibit GBA2 and to a lesser extend GBA1. In the context of the studies that led to the identification of MZ-21 **2** and MZ-31 **3**, it was observed that *N*-neopentyloxypentyl-DNJ **4** and *N*-neopentyloxypentyl-L-*ido*-DNJ **5**, compounds with comparatively (in relation to **2** and **3**) smaller *N*-alkyl substituents, are potent GBA2 inhibitors with comparatively less activity against GCS and GBA1. Compared with MZ-21 ($IC_{50\,GCS}$ / $IC_{50\,GBA2}$ = 235), compound **4** has a much better GBA2 selectivity ($IC_{50\,GCS}$ / $IC_{50\,GBA2}$ = 1020). Compounds **4** and **5** are nanomolar GBA2 inhibitors while inhibiting GCS and GBA1 only in the micromole range, if at all.

Figure 3: *Structure of the lead N-neopentyloxypentyl-DNJ derivatives* ***4*** *(D-glucose configuration) and* ***5*** *(L-idose configuration)*



Taking compounds **4** and **5** as lead structures and with the aim to investigate whether GBA2 selective inhibitors could be designed, a series D-*gluco* and L-*ido*-DNJ derivatives bearing a variety of aliphatic and aromatic *N*-alkyl substituents (Figure 4) were prepared and evaluated on their potency and selectivity (as compared to GCS and GBA1) as GBA2 inhibitors.

Figure 4*: D-Gluco and L-ido-DNJ derivatives subject of the here presented studies*



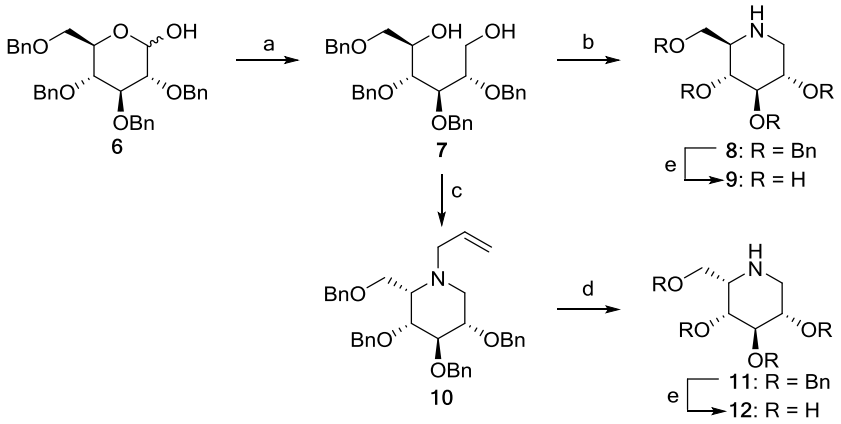
Results and discussion

The synthesis of DNJ (**9**) was accomplished following the established procedure with as key step a double reductive amination of a glucose-derived 5-keto-aldehyde (scheme 1).[16] In the first step, the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**) was reduced to give partially protected glucitol **7**. Swern oxidation of both the primary and secondary alcohol in **7** followed by double reductive amination gave 2,3,4,6-tetra-*O*-benzyl-DNJ (**8**). Catalytic hydrogenation gave DNJ (**9**) in good yield and sufficient quantities for further elaboration.

Treatment of glucitol **7** with excess methanesulfonyl chloride followed by treatment with allyl amine gave, with inversion of configuration at the carbon bearing the secondary alcohol, fully protected L-*ido*-DNJ **10** in good overall yield. The allyl protecting group in **10** was removed by potassium *tert*-butoxide induced isomerization and subsequent acid-catalysed hydrolysis of

the obtained enamine to give **11** in excellent yield. Compound **11** was globally deprotected (H_2, Pd/C) to give L-*ido*-DNJ **12** for ensuing *N*-alkylation.

Scheme 1: *Synthesis of 1-deoxynojirimycin and L-ido-1-deoxynojirimycin*

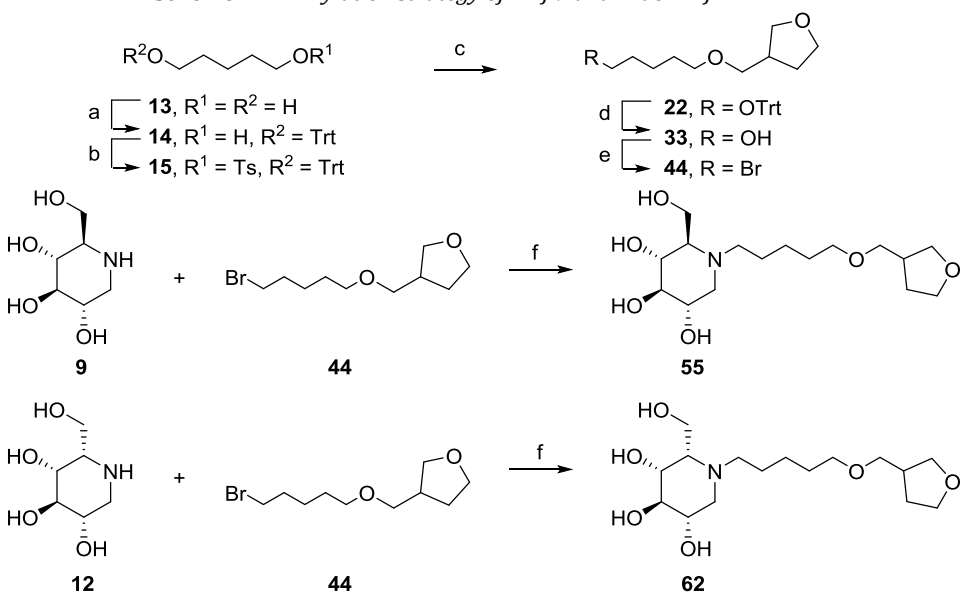


Reagents and conditions: [**a**] $LiAlH_4$, THF; [**b**] 1) $(COCl)_2$, DMSO, DCM; 2) $HCOONH_4$, Na_2SO_4, $NaBH_3CN$, MeOH, 12% 2 steps; [**c**] MsCl, pyridine, allyl amine, reflux, 78% 2 steps; [**d**] *t*BuOK, DMSO, HCl, 92%; [**e**] Pd/C, H_2, 82% (**9**), 76% (**12**).

The synthesis of appropriately functionalized alkylating agents for preparation of the target compounds was accomplished following established procedures. As an example, the synthesis of tetrahydrofuran-3-ylmethyloxypentyl bromide and its use in the *N*-alkylation of DNJ **9** and L-*ido*-DNJ **12** is depicted in Scheme 2. Thus, 1,5-pentanediol (**13**) was treated with one equivalent of trityl chloride (TrtCl) and base, after which the remaining primary alcohol in **14** was transformed into the sulfonate after reacting with *p*-toluenesulfonyl chloride (*p*-TsCl). The tosylate in the thus produced compound **15** was substituted by tetrahydrofuran-3-ylmethyl alcohol, yielding ether **22**. The trityl group in **22** was removed and the resulting alcohol **33** subjected to Appel bromination (treatment with triphenylphosphine and tetrabromomethane) to give bromide **44**. In a similar fashion, all compounds listed in Figure 5 were prepared. Finally, treatment of DNJ **9** with **44** and diisopropyl ethylamine in DMF gave *N*-alkyl-DNJ derivative **55**, and in a similar vein L-*ido*-DNJ derivative **62** was prepared (see experimental for details on the alkyl bromide syntheses and ensuing *N*-alkylation of DNJ **9** and L-*ido*-DNJ **12**).

In a similar way, and in yields varying from 10% up to 88%, *N*-alkyl-DNJ derivatives **4**, **49** - **59** and *N*-alkyl-L-*ido*-DNJ **5**, **60** - **65** were synthesized (Figure 6).

Scheme 2: *N-Alkylation strategy of DNJ* ***9*** *and L-ido-DNJ* ***12***



Reagents and conditions: [**a**] TrtCl, TEA, EtOAc, 85 °C, 3h, 99%; [**b**] *p*-TsCl, TEA, DMAP, DCM, 0 °C to r.t., 2h, 70%; [**c**] 1) THF-3-ylmethanol, NaH, DMF, r.t., 90 min; 2) **15**, 75 °C, 1h, 56%; [**d**] $BF_3{\cdot}OEt_2$, toluene/MeOH (1:1), 1.5h, 72%; [**e**] 1) PPh_3, DCM, r.t., 0 °C; 2) CBr_4, Ar, 2h, 91%; [**f**] DMF, K_2CO_3, 80 °C, 88% (**55**), 30% (**62**).

Figure 5*: Yields of the syntheses of the alkylating agents and their precursors*

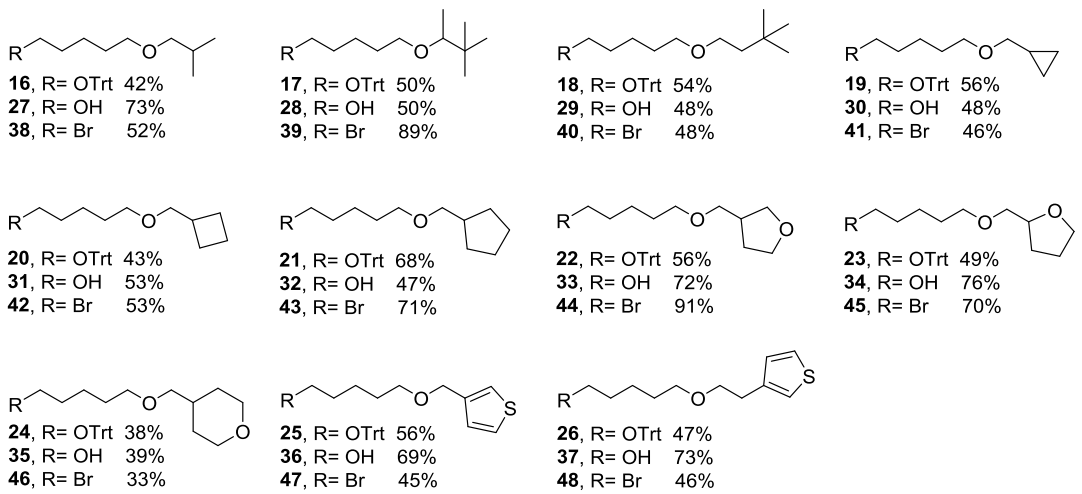
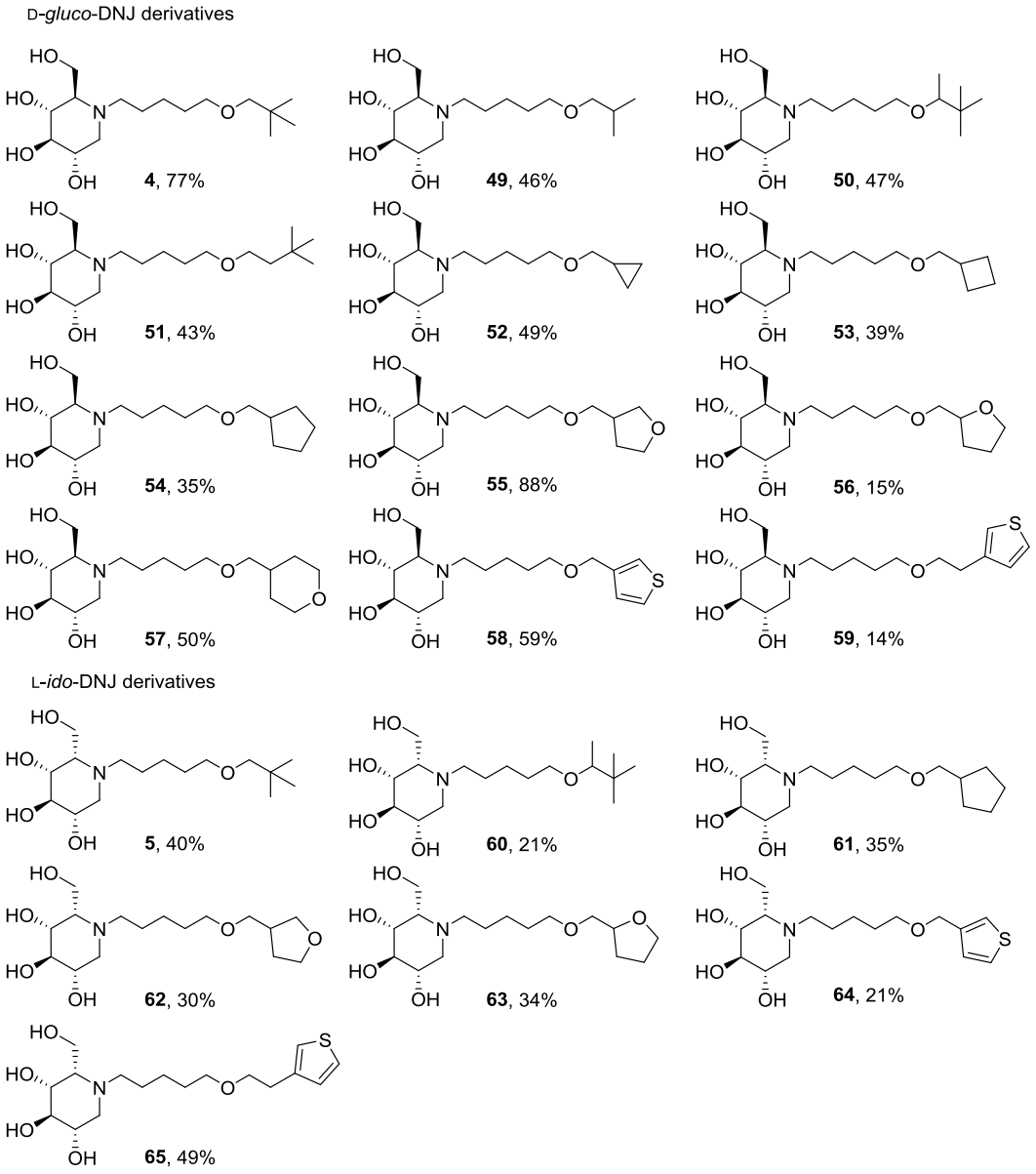


***Figure 6**: Isolated yields of the N-alkylated D-gluco and L-ido iminosugars*



Inhibition activity

Table 1 shows the inhibitory results of lead structure **4** together with *N*-alkyl-DNJ derivatives (**49** - **59**) on the three enzymes involved in glycosylceramide metabolism: GCS, GBA1 and GBA2. From the results on the series of branched alkyl analogues (**49** - **51**), it can be observed that extending the neopentyl group in **4** with one carbon, as in **51**, results in more potent GCS inhibitory activity. The absence (**49**) or presence (**50**) of an additional methyl

moiety gave no significant difference in inhibitory potency towards GCS, compared to **4**. Within the cycloalkyl series (**52** - **54**), the compound with the largest substituent proved to be the most potent GCS inhibitor (inhibitory activity: **54** > **53** > **52**), whereas the tetrahydrofuran- and tetrahydropyran-modified DNJ derivatives **55** - **57** proved to be poor GCS inhibitors. The thiophene containing iminosugars (**58** and **59**) inhibit GCS almost as potently as the literature compound, MZ-21 (**4**). Amongst all the compounds, cyclopentyl-DNJ derivative **54** appeared the most potent GCS inhibitor (IC_{50} = 0.12), whereas compounds **51**, **53**, **58** and **59** are also potent GCS inhibitors with sub-micromolar IC_{50} values. Altogether, these results indicate that a sizeable hydrophobic nonpolar *N*-alkyl group is critical for GCS activity.

***Table 1**: GCS, GBA1 and GBA2 IC_{50} values of the alkylated D-gluco iminosugars*

Compound	*IC_{50} GCS (μM)*	*IC_{50} GBA1 (μM)*	*IC_{50} GBA2 (nM)*
D-*gluco*-DNJ series			
4	5 ± 0.9	6 ± 0.4	5 ± 0.07
49	4 ± 0.1	17 ± 1	7 ± 1
50	6 ± 0.9	3 ± 0.2	4 ± 0.2
51	0.8 ± 0.03	4 ± 0.009	5 ± 0.3
52	7 ± 1	51 ± 2	18 ± 0.2
53	0.6 ± 0.03	12 ± 0.2	9 ± 0.9
54	0.1 ± 0.06	6 ± 0.4	4 ± 0.2
55	>50	156 ± 6	42 ± 5
56	>50	325 ± 14	120 ± 8
57	10 ± 0.7	63 ± 2	35 ± 2
58	0.4 ± 0.06	11 ± 0.2	4 ± 0.6
59	0.4 ± 0.05	6 ± 0.2	2 ± 0.1

With respect to GBA1 inhibitory activity, it was observed that with the exception of compounds **50**, **51**, **54** and **59**, most compounds are less potent than lead compound **4**. This may suggest that a nonpolar hydrophobic moiety of a certain size is essential for GBA1 inhibitory activity. Looking at the nature of the alkyloxy substituent, branched alkyl moieties are favorable with respect to GBA1 inhibitory activity (inhibitory potency: **50** > **4** > **49**). From the cycloalkyl series, it can be concluded that the larger the substituent is, the more potent the compound inhibits GBA1 (inhibitory potency: **54** > **53** > **52**). As was observed for GCS inhibition, the tetrahydrofuranyl/tetrahydropyranyl-DNJ derivatives are poor GBA1 inhibitors (compare, for instance, the GBA1 inhibition values measured for cyclopentanyl-DNJ derivative

54 with those obtained for tetrahydrofuranyl-DNJ derivatives **55** and **56**). Another observed trend is that an extra methylene moiety (**4** versus **51**, **58** versus **59**) is beneficial for GBA1 inhibitory activity. The most potent GBA1 inhibitor of this series finally appeared to be compound **50**.

***Table 2**: GCS, GBA1 and GBA2 IC_{50} values of the alkylated L-ido iminosugars*

Compound	*IC_{50} GCS (μM)*	*IC_{50} GBA1 (μM)*	*IC_{50} GBA2 (nM)*
L-*ido*-DNJ series			
5	3 ± 0.1	>1000	10 ± 0.3
60	5 ± 0.1	196 ± 15	7 ± 0.5
61	0.12 ± 0.005	176 ± 16	3 ± 0.1
62	1 ± 0.2	>1000	25 ± 0.7
63	2.5 ± 0.4	>1000	21 ± 4
64	0.05 ± 0.002	328 ± 26	2 ± 0.3
65	0.12 ± 0.008	205 ± 0.4	11 ± 0.04

Looking at GBA2 inhibitory activity, finally, it can be seen that all *N*-alkyl-DNJ derivatives tested are potent GBA2 inhibitors. Again, compounds **55**, **56**, and **57** featuring a tetrahydrofuranyl/tetrahydropyranyl moiety are the weakest inhibitors of the series. However, GBA2 inhibitory activity is less affected by the presence of an oxygen atom than GBA1 and GCS inhibitory activities. When comparing tetrahydrofuranyl-DNJ **55** with cyclopentyl-DNJ **54**, it can be seen that substituting one of the cyclopentyl carbons (as in **54**) for oxygen (as in **55**) led to a 500-fold decrease in GCS inhibitory activity, a 25-fold decrease in GBA1 inhibitory activity, and a 10-fold decrease in GBA2 inhibitory activity. Thus, while compound **55** is less potent than carbon analogue **54**, it is the more selective GBA2 inhibitor. Amongst the cycloalkyl-DNJ derivatives, compound **54** featuring a cyclopentane moiety appeared to be the most potent GBA2 inhibitor.

In summary on this part, DNJ derivative **55** appears to be the most GBA2 selective compound ($IC_{50\,GCS}$ / $IC_{50\,GBA2}$ = 1176, $IC_{50\,GBA1}$ / $IC_{50\,GBA2}$ = 3682), and while less active it is also more selective than compound **4**, which served as the starting point of the here-presented studies ($IC_{50\,GCS}$ / $IC_{50\,GBA2}$ = 1020, $IC_{50\,GBA1}$ / $IC_{50\,GBA2}$ = 1252). At the same time, all DNJ derivatives follow the general trend that, in case GCS is inhibited, also GBA1 is inhibited with considerable potency. As has been shown before, altering the configuration of the piperidine moiety from D-glucose to L-idose can abolish GBA1 inhibition.

Accordingly, a number of alkyl substituents were selected and the corresponding *N*-alkyl-L-*ido*-DNJ derivatives were prepared (Scheme 2) and evaluated (Table 2) as GCS/GBA1/GBA2 inhibitors. As *N*-alkyl moieties, the most effective substituents from the D-*gluco*-DNJ series in terms of activity and selectivity were selected, leading to compounds **60** – **65**, the inhibitory potency of which was compared with lead L-*ido*-DNJ derivative **5**. All L-*ido* derivatives tested are more potent GCS inhibitors in comparison with their D-*gluco* congeners. This follows the trend witnessed in earlier studies, and the same holds true for GBA1 inhibition (all L-*ido*-DNJ derivatives tested are considerably weaker GBA1 inhibitors compared to the D-*gluco*-DNJ analogues). Finally and importantly, there is not much difference between GBA2 inhibitory potency when going from a D-*gluco*-DNJ derivative to its configurational L-*ido*-DNJ derivative (compare the GBA2 inhibitory potency of **60** with that of **50**; **61** with **54**; **62** with **55**; **63** with **56**; **64** with **58**; and **65** with **59**). Hence all L-*ido*-DNJ derivatives tested are potent GCS/GBA2 inhibitors with a considerable therapeutic window towards GBA1 – the enzyme one would like to avoid targeting when aiming for the development of new and improved substrate reduction therapies for Gaucher patients. Amongst the compounds tested thiophene-DNJ derivative **64** appears to be the most potent analogue and further testing of this compound in relevant biological systems may be considered.

Conclusion

In this Chapter 17 new *N*-alkyl-DNJ derivatives are described, the structures of which are inspired by neopentyl-DNJ derivatives **4** and **5**. From the compounds tested, DNJ derivative **55** may well be the most selective, nanomolar GBA2 inhibitor reported to date. The most potent GBA2 inhibitors in turn appear to be **59** and **64.** These compounds, as well as thiophene-L-*ido*-DNJ derivative **58**, which came out as the most most potent GCS inhibitor, deserves more in-depth studies with respect to their *in situ* and even *in vivo* efficacy to modulate GlcCer metabolism through inhibition of GCS and/or GBA2.

Experimental Section

Enzyme inhibition assays: The potencies (IC_{50} values) of the *N*-alkyl-DNJ derivatives as GCS, GBA1 and GBA2 inhibitors were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[17] Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon

phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbeliferyl-β-D-glucoside as substrate.[18] Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and sodium taurocholate (0.2%, w/v). Assays performed in triplicate were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm.

GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with 4-methylumbeliferyl-β-D-glucoside as substrate.[18] GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbeliferyl-β-D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General compound synthesis, purification and analysis methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz) or Bruker 600 (600/150 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[19] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ =589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer, column size d = 26 mm, l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 μm, 19 x 150 mm column).

General procedure A: Substitution of the tosyl group. A dry solution of alcohol (5 mmol) in DMF (15 mL) was charged with NaH (10 mmol) and stirred for 90 min. Then a dry solution of **15** (4.5 mmol) in DMF (15 mL) was added. The reaction mixture was heated to 75 °C for 1 h.

After complete consumption of the starting material (TLC monitored), the mixture was cooled to room temperature, quenched by the addition of water (3 mL) and concentrated. The residue was dissolved in a mixture of TEAA (0.1 M), EtOAc and sat. aq. $NaHCO_3$ (80 mL, 2:3:3) and extracted with EtOAc (3 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by silica gel column chromatography (0 - 10% EtOAc in PE) gave the target compound.

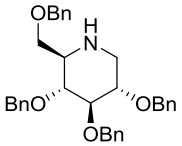
General Procedure B: Deprotection of the trityl-group. To a solution of alkyloxyl-1-trityloxpentane (2.0 mmol) in toluene/MeOH (1:1, 20 mL, 0.1 M) was added $BF_3{\cdot}Et_2O$ (3.0 mmol, 1.5 eq). This mixture was stirred for 1.5 h at r.t. After complete consumption of the starting material (TLC monitored), the mixture was diluted with EtOAc (30 mL) and washed with sat. aq. $NaHCO_3$ (50 mL). The water layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and the residue purified by silica gel column chromatography (1:9 → 1:4 → 1:1 → 1:0, EtOAc:PE) to give target alcohol chain.

General Procedure C: Bromination. To a solution of alkyloxyl-1-pentanol (1 mmol) in DCM (100 mL, 0.01 M) was added PPh_3 (0.40 g, 1.5 mmol, 1.5 eq) and cooled to 0 °C. Then CBr_4 (0.5 g, 1.5 mmol, 1.5 eq) was added and the reaction mixture was stirred at 0 °C until TLC analysis monitored the complete consumption of starting compound. After which Celite was added and the volatiles were evaporated. The residue was purified with silica gel column chromatography (0 - 100% toluene in heptane → 2 - 20% EtOAc in toluene) to give the bromide spacer.

General Procedure D: Alkylation of iminosugars. To a mixture of the 1-bromo-5-alkyloxy-pentane (0.3 mmol, 1.5 eq) and di-isopropylethylamine (DiPEA, 0.1 mL, 0.6 mmol, 3 eq) was added a solution of iminosugar (0.03 g, 0.2 mmol) in DMF (1 mL). The mixture was stirred overnight at 70 °C. After cooling to r.t., the mixture was filtered and concentrated. The crude product was purified using HPLC.

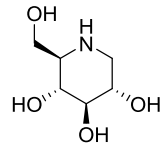
Synthesis of DNJ and L-*ido*-DNJ

2,3,4,6-Tetra-*O*-benzyl-1-deoxynojirimycin (8):



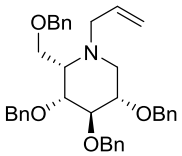
A solution of $(COCl)_2$ (0.70 mL, 8.16 mmol) in dry DCM (5 mL) under argon atmosphere, was cooled to -78 °C. DMSO (0.71 mL, 10.0 mmol) dissolved in dry DCM (5 mL) was added dropwise. After 40 minutes, **7** (1.02 g, 1.88 mmol, co-evaporated with toluene 3 x) in dry DCM (3 mL), was added dropwise to the mixture. The reaction was stirred for 2 hours at -78 °C, after which Et_3N (3.40 mL, 24.4 mmol) was added dropwise. The mixture was gradually warmed to -5 °C after which it was poured into a cooled (0 °C) MeOH solution (50 mL) containing $NaCNBH_3$ (0.50 g, 8.00 mmol), $HCOONH_4$ (2.53 g, 40.1 mmol), and Na_2SO_4 (0.89 g, 6.24 mmol). The mixture was stirred overnight during which the reaction mixture was allowed to warm up to r.t. TLC analysis showed complete consumption of the starting material (1:1, PE:EtOAc, R_F = 0.36). After filtration, the volatiles were evaporated, and the residue was dissolved in EtOAc (70 mL), washed with sat. aq. $NaHCO_3$ (70 mL). The organic layer was dried (Na_2SO_4) filtrated and concentrated. The residue was purified with silica gel column chromatography (2:1 → 1:2, PE:EtOAc) to give the pure product **8** in 12% overall yield (0.114 g, 0.218 mmol). R_F = 0.36 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 20H, H_{Ar} Bn), 5.00 – 4.38 (m, 8H, 4 x CH_2 Bn), 3.66 (dd, *J* = 9.0, 2.5 Hz, 1H, H-6a), 3.58 – 3.44 (m, 3H, H-2, H-3, H-6b), 3.35 (t, *J* = 9.2 Hz, 1H, H-4), 3.23 (dd, *J* = 12.3, 4.9 Hz, 1H, H-1a), 2.71 (ddd, *J* = 9.7, 5.9, 2.6 Hz, 1H, H-5), 2.49 (dd, *J* = 12.2, 10.3 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9 – 138.0 (C_q Bn), 128.4 – 127.6 (CH_{Ar} Bn), 87.3 (C-3), 80.6 (C-2), 80.1 (C-4), 75.7, 75.2, 73.4, 72.8 (4 x CH_2 Bn), 70.2 (C-6), 59.8 (C-5), 48.1 (C-1).

1-Deoxynojirimycin (9):



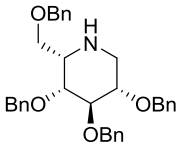
8 (2.00 g, 3.82 mmol) was dissolved in EtOH (120 mL) and pH was adjusted to 2 with HCl solution (1 M). The solution was flushed with argon (3 x), after which two spatula tips of Pd/C (20%) was added. Then the mixture was exposed to H_2 atmosphere (4 bar) for 24 hours. The catalyst was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified on silica gel column chromatography (4:1, EtOAc:MeOH + 1% NH_4OH → 6:4:1, EtOH:H_2O:NH_4OH) to give **9** in 82% yield (511 mg, 3.13 mmol). ^{1}H NMR (400 MHz, MeOD) δ 3.92 (dd, *J* = 10.9, 3.1 Hz, 1H, H-6a), 3.67 (dd, *J* = 10.9, 6.5 Hz, 1H, H-6b), 3.49 (ddd, *J* = 10.6, 8.7, 5.1 Hz, 1H, H-2), 3.28 (t, *J* = 8.1 Hz, 1H, H-3), 3.24 (t, *J* = 9.1 Hz, 1H, H-4), 3.18 (dd, *J* = 12.1, 5.1 Hz, 1H, H-1a), 2.54 (ddd, *J* = 9.4, 6.4, 3.1 Hz, 1H, H-5), 2.52 (dd, *J* = 12.1, 10.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 81.5 (C-3), 74.2 (C-4), 73.5 (C-2), 64.0 (C-6), 63.7 (C-5), 51.9 (C-1).

2,3,4,6-Tetra-*O*-benzyl-L-*ido*-*N*-allyl-1-deoxynojimycin (10):



MsCl (4.2 mL, 53.1 mmol) was added dropwise to a cooled mixture (0 °C) of pyridine (90 mL) and **7** (11.5 g, 21.2 mmol). The mixture was stirred for 3 hours at r.t., after which TLC analysis (2:1, PE:EtOAc, R_F = 0.13) showed complete consumption of the starting material. Water (60 mL) was added and the solution was concentrated. The residue was dissolved in EtOAc (130 mL), and successively washed with HCl (100 mL, 1M, 2 x), sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was co-evaporated with toluene (3 x). Allylamine (90 mL) was added to dissolve the methanesulfonylated product, and the solution was heated to reflux for 14 hours, until TLC analysis (2:1, PE:EtOAc) showed complete consumption of the starting material. After concentration, the residue was dissolved with EtOAc (110 mL), washed with sat. aq. $NaHCO_3$ (100 mL, 2 x) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified on silica gel column chromatography (17:3, PE:EtOAc) to give **10** in 78% yield (9.30 g, 16.5 mmol). R_F = 0.76 (2:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 20H, H_{Ar} Bn), 5.77 (ddt, *J* = 16.8, 10.3, 6.3 Hz, 1H, H-2'), 5.12 (dd, *J* = 23.6, 6.2 Hz, 2H, H-3"), 4.90 – 4.46 (m, 8H, 4 x CH_2 Bn), 3.84 (dd, *J* = 10.2, 6.8 Hz, 1H, H-1a'), 3.72 (dd, *J* = 10.2, 2.5 Hz, 1H, H-1b"), 3.69 (dd, *J* = 7.6, 4.2 Hz, 1H, H-4), 3.60 – 3.50 (m, 2H, H-2, H-3), 3.42 (ddd, *J* = 10.1, 5.8, 1.6 Hz, 1H, H-5), 3.37 (dd, *J* = 6.9, 2.0 Hz, 1H, H-6a), 3.18 (dd, *J* = 14.1, 6.9 Hz, 1H. H-6b), 2.92 (dd, *J* = 11.9, 4.9 Hz, 1H, H-1a), 2.53 (dd, *J* = 11.8, 9.8 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.8, 138.7, 138.6 (4 x C_q Bn), 136.3 (C-2"), 128.5 – 127.6 (CH_{Ar} Bn), 117.2 (C-3"), 83.1 (C-4), 80.2 (C-3), 78.9 (C-2), 75.5, 73.4, 73.1 72.8 (4 x CH_2 Bn), 64.7 (C-1"), 60.1 (C-5), 58.1 (C-6), 49.1 (C-1).

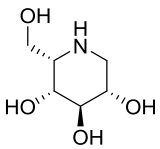
2,3,4,6-Tetra-*O*-benzyl-L-*ido*-1-deoxynojimycin (11):



A mixture of DMSO (35 mL), *t*BuOK (1.00 g, 8.91 mmol) and **10** (9.30 g, 16.5 mmol, co-evaporated with toluene 3 x) was heated to 100 °C and stirred under argon atmosphere. After 1 hour stirring, HCl solution (30 mL, 1M) was added and the heating resource was removed. After 30 minutes, the mixture was poured into a mixture of sat. aq. $NaHCO_3$ (100 mL) and Et_2O (150 mL). The organic layer was separated and the water layer was re-extracted with Et_2O (150 mL, 2 x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified with silica gel column chromatography (2:1 → 1:2 → 0:1, PE:EtOAc) to give the pure product **11** with a yield of 92% (7.93 g, 15.1 mmol). R_F = 0.13 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 20H, H_{Ar} Bn), 4.68 – 4.49 (m, 8H, 4 x CH_2 Bn), 3.68 (t, *J* = 9.2 Hz, 1H, H-6a), 3.62 (t, *J* = 5.3 Hz, 1H, H-3), 3.55 (dd, *J* = 9.5, 5.2 Hz, 1H, H-6b), 3.45 (td, *J* = 6.6, 4.1 Hz, 1H, H-2), 3.38 (ddd, *J* = 8.7, 5.0, 3.6 Hz, 1H, H-5), 3.01 (dd, *J* = 12.9, 4.1 Hz, 1H, H-1a), 2.86 (dd, J = 12.8, 6.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 – 138.4 (C_q Bn), 128.5 – 127.7 (CH_{Ar}

Bn), 77.3 (C-3), 77.0 (C-2), 74.2 (CH_2 Bn), 73.5 (CH_2 Bn), 72.7 (CH_2 Bn), 72.2 (CH_2 Bn), 67.3 (C-6), 54.7 (C-5), 44.3 (C-1).

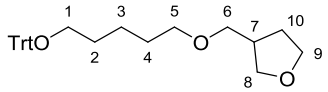
L-*Ido*-1-deoxynojimycin (12):



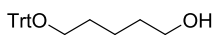
11 (2.30 g, 4.39 mmol) was dissolved in EtOH (150 mL) and pH was adjusted to 2 with HCl solution (1 M). The solution was flushed with argon for 3 times, after which two spatula tips of Pd/C (20%) was added. The suspension was exposed to H_2 atmosphere (4 bar) and shaken for 24 hours. The catalyst was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified with silica gel column chromatography (4:1 EtOAc:MeOH + 1% NH_4OH → 6:4:1, EtOH: H_2O:NH_4OH) to give the **12** in 76% yield (840 mg, 3.32 mmol). ^{1}H NMR (400 MHz, MeOD) δ 3.95 – 3.93 (m, 2H, H-2, H-3), 3.89 (dd, *J* = 5.7, 2.0 Hz, 1H, H-4), 3.85 (dd, *J* = 11.0, 2.1 Hz, 1H, H-6a), 3.81 (dd, *J* = 11.7, 5.1 Hz, 1H, H-6b), 3.47 (ddd, *J* = 8.9, 5.0, 1.9 Hz, 1H, H-5), 3.36 (dd, *J* = 13.2, 2.0 Hz, 1H, H-1a), 3.24 (dd, *J* = 13.2, 1.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 69.2 (C-4), 68.4 (C-3), 68.0 (C-2), 60.3 (C-6), 58.2 (C-5), 46.9 (C-1).

Synthesis of the bromide-spacers

***Figure 7**: Proton and carbon NMR numbering of the linker molecules (**16**- **48**)*

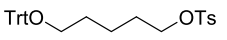


5-Trityloxy-1-pentanol (14):



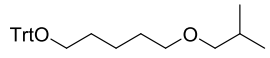
Trityl chloride (55.82 g, 200 mmol), 1,5-pentanediol (100 mL, 954 mmol), EtOAc (500 mL) and TEA (56 mL, 396 mmol) were mixed. The mixture was stirred for 3h at 85 °C. After complete conversion of the starting material (1:1, PE:EtOAc) the mixture was washed successively with HCl (4 x 100 mL, 1M) and sat. aq. $NaHCO_3$ (4 x 100 mL), dried ($MgSO_4$) and concentrated to give compound **22** (68.67 g, 198.20 mmol, 99% yield). R_F = 0.70 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 6H, H_{Ar} Trt), 7.29 – 7.17 (m, 9H, H_{Ar} Trt), 3.57 – 3.55 (m, 2H, H_2-1), 3.07 – 3.05 (m, 2H, H_2-5), 1.65 – 1.63 (m, 2H, H_2-4), 1.55 – 1.35 (m, 4H, H_2-2, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4 (C_q Trt), 128.6 – 126.8 (CH Trt), 86.3 (C_q Trt), 63.4 (C-1), 62.7 (C-5), 32.5 (C-4), 29.7 (C-2), 22.4 (C-3).

5-(Toluene-4-sulfonyl)-1-trityloxypentane (15):



p-Toluenesulfonyl chloride (8.83 g, 46.3 mmol) was added to a dry and cooled (0 °C) mixture of **14** (10.72 g, 30.94 mmol), TEA (7 mL, 49.5 mmol) and DMAP (0.19 g, 1.56 mmol) in DCM (93 mL). The mixture was stirred for 2h while warming to r.t. The mixture was washed successively with HCl (100 mL, 1M), sat. aq. $NaHCO_3$ (100 mL) and sat. aq. NaCl (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification of the residue with silica gel column chromatography (10 – 16% EtOAc in PE) gave compound **15** (10.9 g, 21.7 mmol, 70%) as a white solid. R_F = 0.78 (25% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, H_{Ar} Ts), 7.42 (d, 6H, H_{Ar} Trt), 7.24 – 7.19 (m, 10H, H_{Ar} Trt/Ts), 7.16 – 7.13 (m, 3H, H_{Ar} Trt), 3.94 (t, 2H, H-5), 3.00 (t, 2H, H_2-1), 1.94 (s, 3H, CH_3 Ts), 1.54 – 1.49 (m, 4H, H_2-2, H_2-4), 1.35 – 1.33 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (C_q Ts), 144.5(C_q Trt), 133.3(C_q Ts), 130.0 (CH, Ts), 128.9 – 127.1 (CH Trt), 86.5 (C_q Trt), 70.7 (C-5), 63.2(C-1), 29.4 (C-2), 28.7 (C-4), 22.4 (C-3), 21.7 (CH_3 Ts).

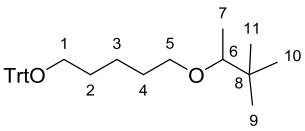
5-(2-Methyl-1-propyloxy)-1-trityloxypentane (16):



Compound **15** (4.60 mmol) was subjected to the general procedure A, using 2-methyl-1-propanol (5.05 mmol) to provide **16** (0.77 g, 1.92

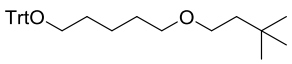
mmol) in a yield of 42%, as thick oil, after silica gel column chromatography purification. R_F = 0.65 (10% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, *J* = 8.6, 2.2, 1.6 Hz, 6H, H_{Ar} Trt), 7.32 – 7.14 (m, 9H, H_{Ar} Trt), 3.37 (t, *J* = 6.5 Hz, 2H, H_2-5), 3.14 (d, *J* = 6.8 Hz, 2H, H_2-6), 3.06 (t, *J* = 6.6 Hz, 2H, H_2-1), 1.84 (dp, *J* = 6.7 Hz, 1H, H-7), 1.71 – 1.60 (m, 2H, H_2-2), 1.59 – 1.50 (m, 2H, H_2-4), 1.50 – 1.37 (m, 2H, H_2-3), 0.89 (d, *J* = 6.7 Hz, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_q Trt), 128.8 (CH Trt), 127.7 (CH Trt), 126.9 (CH Trt), 86,4 (C_q Trt), 77.9 (C-6), 71.0 (C-5), 63.6 (C-1), 30.0 (C-2), 29.7 (C-4), 28.5 (C-7), 23.1 (C-3), 19.5 (2 x CH_3). IR/cm^{-1}: 3061, 2930, 2901, 2866, 1597, 1489, 1448, 1392, 1364, 1176, 1072.

5-(3,3-Dimethyl-2-butoxy)-1-trityloxypentane (17):



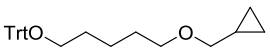
Compound **15** (4.43 mmol) was subjected to the general procedure A, using 3,3-dimethyl-2-butanol (5.06 mmol) to provide **17** (0.95 g, 2.21 mmol) in a 50% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.79 (5% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 6H, H_{Ar} Trt), 7.28 – 7.11 (m, 12H, H_{Ar} Trt), 3.53 (dt, *J* = 9.4, 5.8 Hz, 1H, H-5a), 3.21 (dd, *J* = 9.2, 6.2 Hz, 1H, H-5b), 3.06 (t, *J* = 6.6 Hz, 2H, H_2-1), 2.93 (q, *J* = 6.3 Hz, 1H, H-6), 1.74 – 1.35 (m, 6H, H_2-2, H_2-3, H_2-4), 1.01 (d, *J* = 6.3 Hz, 3H, H_3-7), 0.87 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C_q Trt), 128.8 (CH Trt), 127.9 (CH Trt), 126.9 (CH Trt), 86.4 (C_q Trt), 83.4 (C-6), 69.8 (C-5), 63.7 (C-1), 35.3 (C-8), 30.3 (C-2), 30.1 (C-4), 26.2 (C-7), 23.3 (C-3), 14.1 (C-9, C-10, C-11). IR/cm^{-1}: 3059, 3022, 2936, 2866, 1597, 1489, 1448, 1389, 1362, 1219, 1090, 1072.

5-(3,3-Dimethyl-1-butoxy)-1-trityloxypentane (18):



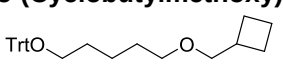
Compound **15** (4.41 mmol) was subjected to the general procedure A, using 3,3-dimethyl-1-butanol (5.07 mmol) to provide **18** (1.02 g, 2.36 mmol) in a 54% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.67 (5% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 8.3, 2.2 Hz, 6H, H_{Ar} Trt), 7.25 – 7.16 (m, 6H, H_{Ar} Trt), 7.16 – 7.10 (m, 3H, H_{Ar} Trt), 3.41 (t, *J* = 7.4 Hz, 2H, H_2-5), 3.34 (t, *J* = 6.4 Hz, 2H, H_2-6), 3.06 (td, *J* = 6.9, 3.0 Hz, 2H, H_2-1), 1.63 (p, *J* = 6.8 Hz, 2H, H_2-2), 1.52 (m, 4H, H_2-4, H_2-7), 1.48 - 1.38 (m, 2H, H_2-3), 0.90 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C_q Trt), 128.7 (C_{Ar} Trt), 127.7 (CH Trt), 126.8 (CH Trt), 86.3 (C_q Trt), 70.8 (C-6), 68.1 (C-5), 63.5 (C-1), 43.0 (C-7), 29.8 (C-2), 29.7 (C-9,10,11), 29.6 (C-4), 29.6 (C-8), 23.1 (C-3). IR/cm^{-1}: 3057, 3022, 2936, 2864, 1597, 1489, 1448, 1364, 1219, 1111, 1072.

5-(Cyclopropylmethoxy)-1-trityloxypentane (19):



Compound **15** (4.41 mmol) was subjected to the general procedure A, using cyclopropylmethanol (5.02 mmol) to provide **19** (0.10 g, 2.49 mmol) in a 56% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.63 (10% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 6H, Trt), 7.28 - 7.19 (m, 6H, H_{Ar} Trt), 7.20 – 7.13 (m, 3H, H_{Ar} Trt), 3.38 (t, *J* = 6.6 Hz, 2H, H_2-5), 3.20 (d, *J* = 6.9 Hz, 2H, H_2-6), 3.06 (t, *J* = 6.6 Hz, 2H, H_2-1), 1.65 (p, *J* = 6.8 Hz, 2H, H_2-2), 1.51 – 1.59 (m, 2H, H_2-4), 1.47 – 1.38 (m, 2H, H_2-3), 1.08 – 0.97 (m, 1H, H-7), 0.52 – 0.45 (m, 2H, H_2-8), 0.16 (dt, *J* = 6.0, 4.5 Hz, 2H, H_2-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_q Trt), 128.8 (CH Trt), 127.8 (CH Trt), 126.9 (CH Trt), 86.4 (C_q Trt), 75.7 (C-7), 70.7 (C-5), 63.7 (C-1), 30.1 (C-2), 29.8 (C-4), 23.1 (C-3), 10.8 (C-7), 3.2 (C-8, C-9). IR/cm^{-1}: 3082, 3057, 3022, 2933, 2862, 1732, 1597, 1489, 1448, 1382, 1219, 1087, 1074.

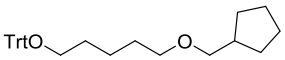
5-(Cyclobutylmethoxy)-1-trityloxypentane (20):



Compound **15** (4.40 mmol) was subjected to the general procedure A, using cyclobutylmethanol (5.01 mmol) to provide **20** (0.79 g, 1.91 mmol) in a 43% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.74 (10% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 6H, H_{Ar} Trt) 7.22 – 7.17 (m, 6H,

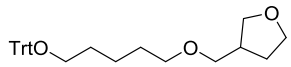
H_{Ar} Trt), 7.14 – 7.10 (m, 3H, H_{Ar} Trt), 3.37 – 3.32 (m, 4H, H_2-5, H_2-6), 3.07 (t, 2H, H_2-1), 2.56 – 2.49 (m, 1H, C-7), 2.04 – 1.97 (m, 2H, H_2-10), 1.86 – 1.79 (m, 2H, H_2-8), 1.75 – 1.40 (m, 8H, H_2-9. H_2-2, H_2-4, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_q Trt), 128.9 (CH Trt), 127.9 (CH Trt), 127.0 (CH Trt), 86.5 (C_q Trt), 75.6 (C-6), 71.1 (C-5), 63.7 (C-1), 35.4 (C-7), 29.9 (C-2), 29.8 (C-4), 25.4 (C-8, C-10), 23.2 (C-3), 18.9 (C-9). IR/cm^{-1}: 3084, 3059, 2934, 2862, 1597, 1489, 1448, 1363, 1219, 1111, 1072.

5-(Cyclopentylmethoxy)-1-trityloxypentane (21):



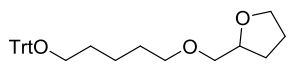
Compound **15** (4.43 mmol) was subjected to the general procedure A, using cyclopentylmethanol (5.09 mmol) to provide **21** (1.29 g, 3.02 mmol) in a 68% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.77 (10% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 6H, H_{Ar} Trt), 7.18 – 7.06 (m, 9H, H_{Ar} Trt), 3.39 – 3.29 (m, 2H, H_2-5), 3.21 (dd, *J* = 7.0, 1.0 Hz, 2H, H_2-6), 3.05 (dt, *J* = 11.1, 6.5 Hz, 2H, H_2-1), 2.10 (q, *J* = 7.4 Hz, 1H, H_2-7), 1.74 – 1.57 (m, 4H, H_2-8, H_2-11), 1.57 – 1.36 (m, 8H, H_2-2, H_2-3, H_2-4, H_2-9), 1.31 – 1.17 (m, 2H, H_2-10). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4 – 125.6 (CH Trt), 75.2 (C-6), 70.6 (C-5), 63.3 (C-1), 38.4 (C-7), 29.4 – 28.7 (C-8, C-9, C-10, C-11), 25.3, 25.1 (C-2, C-4), 22.8 (C-3). IR/cm^{-1}: 3084, 3057, 3022, 2939, 2864, 1597, 1489, 1448, 1367, 1176, 1072.

5-(*R*/*S*-Tetrahydrofuran-3-ylmethoxy)-1-trityloxypentane (22):



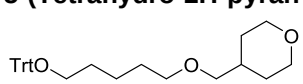
Compound **15** (4.61 mmol) was subjected to the general procedure A, using *R/S* tetrahydrofuran-3-ylmethanol (4.96 mmol) to provide **22** (1.11 g, 2.58 mmol) in a 56% yield, as an oil, after silica gel column chromatography purification. R_F = 0.40 (15% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 6H, H_{Ar} Trt), 7.21 (dd, *J* = 8.5, 6.8 Hz, 6H, H_{Ar} Trt), 7.16 – 7.10 (m, 3H, H_{Ar} Trt), 3.75 (ddd, *J* = 12.1, 8.3, 6.2 Hz, 2H, H-8a, H-9a), 3.68 - 3.55 (m, 1H, H-8b), 3.53 (dd, *J* = 8.7, 5.4 Hz, 1H, H-9b), 3.40 – 3.18 (m, 4H, H_2-5, H_2-9), 3.07 (t, *J* = 6.5 Hz, 2H, H_2-1), 2.49 – 2.35 (m, 1H, H-7), 1.87 (ddt, *J* = 13.9, 8.1, 4.0 Hz, 1H, H-10a), 1.62 (p, *J* = 6.8 Hz, 2H, H_2-2), 1.51 (m, 3H, H_2-4, H-10b), 1.46 – 1.37 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_q Trt), 128.8 (CH Trt), 127.0 (CH Trt), 86.4 (C_q Trt), 73.0 (C-8), 71.1 (C-5), 71.1 (C-9), 67.8 (C-7), 39.4 (C-1), 30.0 (C-10), 29.6 (C-2), 29.2 (C-4), 23.1 (C-3). IR/cm^{-1}: 3445, 2934, 2866, 2347, 1716, 1489, 1448, 1339, 1163, 1074.

5-(*R*/*S*-Tetrahydrofuran-1-ylmethoxy)-1-trityloxypentane (23):



Compound **15** (5.03 mmol) was subjected to the general procedure A, using *R/S* tetrahydrofuran-1-ylmethanol (5.73 mmol) to provide **23** (1.06 g, 2.46 mmol) in a yield of 49%, as an oil, after silica gel column chromatography purification. R_F = 0.52 (15% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 6H, H_{Ar} Trt), 7.32 – 7.23 (m, 6H, H_{Ar} Trt), 7.23 – 7.16 (m, 3H, H_{Ar} Trt), 4.02 (tt, *J* = 7.3, 5.3 Hz, 1H, H-7), 3.85 (ddd, *J* = 8.2, 6.9, 6.1 Hz, 1H, H-10a), 3.73 (ddd, *J* = 8.2, 7.2, 6.3 Hz, 1H, H-10b), 3.53 – 3.37 (m, 4H, H_2-5, H_2-6), 3.05 (t, *J* = 6.6 Hz, 2H, H_2-1), 1.96 – 1.77 (m, 3H, H_2-2, H-9a), 1.69 – 1.60 (m, 2H, H_2-2), 1.60 – 1.52 (m, 3H, H_2-4, H-9b), 1.47 – 1.37 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C_q Trt), 128.7 (CH Trt), 127.7 (CH Trt), 126.9 (CH Trt), 86.3 (C_q Trt), 77.9 (C-7), 73.6 (C-6), 71.6 (C-5), 68.4(C-10), 63.6 (C-1), 30.0 (C-9), 29.6 (C-4), 28.2 (C-8), 25.7 (C-2), 22.9 (C-3). IR/cm^{-1}: 3084, 3055, 3022, 2934, 2862, 1597, 1489, 1448, 1373, 1219, 1111, 1074.

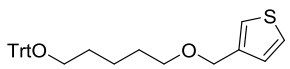
5-(Tetrahydro-2H-pyran-4-ylmethoxy)-1-trityloxypentane (24):



Compound **15** (4.68 mmol) was subjected to the general procedure A, using tetrahydro-2H-pyran-4-ylmethanol (4.34 mmol) to provide **24** (0.79 g, 1.78 mmol) in a yield of 38%, as an oil, after silica gel column chromatography purification. R_F = 0.48 (15% EtOAc in PE). ^{1}H NMR (400 MHz,

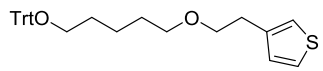
$CDCl_3$) δ 7.48 – 7.35 (m, 6H, H_{Ar} Trt), 7.32 – 7.21 (m, 6H, H_{Ar} Trt), 7.25 – 7.13 (m, 3H, H_{Ar} Trt), 3.99 – 3.89 (m, 2H, H_2-10), 3.42 – 3.30 (m, 4H, H_2-5, H_2-9), 3.21 (d, *J* = 6.6 Hz, 2H, H_2-1), 3.06 (t, *J* = 6.5 Hz, 2H, H_2-6), 1.88 – 1.74 (m, 1H, H-7), 1.70 – 1.57 (m, 4H, H_2-2, H_2-8), 1.57 – 1.47 (m, 2H, H_2-4), 1.47 – 1.38 (m, 2H, H_2-3), 1.35 – 1.25 (m, 2H, H_2-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C_q Trt), 128.7 (CH Trt), 127.7 (CH Trt), 126.9 (CH Trt), 86.4 (C_q Trt), 75.9 (C-6), 71.1 (C-1), 67.7 (C-9, C-10), 63.5 (C-5), 35.5 (C-7), 30.1 (C-8, C-11), 29.9 (C-2), 29.6 (C-4), 23.0 (C-3). IR/cm^{-1}: 3085, 3056, 3023, 2932, 2849, 1558, 1506, 1506, 1489, 1227, 1163, 1097.

5-(Thiophen-3-methoxy)-1-trityloxypentane (25):



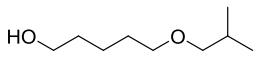
Compound **15** (4.56 mmol) was subjected to the general procedure A, using 3-thiophenmethanol (4.57 mmol) to provide **25** (0.73 g, 2.13 mmol) in a 56% yield, as thick oil, after silica gel column chromatography purification. R_F = 0.79 (15% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 6H, H_{Ar} Trt), 7.28 – 7.20 (m, 6H, H_{Ar} Trt), 7.20 - 7.14 (m, 3H, H_{Ar} Trt), 7.12 (dq, *J* = 3.0, 1.0 Hz, 1H, H thio), 7.04 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 7.02 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 4.44 (d, *J* = 0.8 Hz, 2H, H_2-6), 3.40 (t, *J* = 6.5 Hz, 2H, H_2-5), 3.05 (t, *J* = 6.6 Hz, 2H, H_2-1), 1.70 – 1.49 (m, 4H, H_2-2, H_2-4), 1.51 – 1.36 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_q Trt), , 128.9 (CH Trt), 127.9 (CH Trt), 127.4 (CH thio), 127.0 (C_q Trt), 126.0 (CH thio), 122.6 (CH thio), 114.7 (C_q Thio), 86.5 (C_q Trt), 70.4 (C-5), 68.3 (C-6), 63.7 (C-1), 30.0 (C-2), 29.8 (C-4), 23.1 (C-3). IR/cm^{-1}: 3501, 3088, 3059, 3024, 2938, 2864, 2316, 1734, 1448, 1364, 1242, 1068, 1034.

5-(Thiophen-3-ethoxy)-1-trityloxypentane (26):



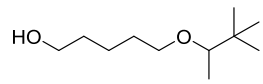
Compound **15** (4.56 mmol) was subjected to the general procedure A, using 3-thiophenethanol (4.57 mmol) to provide **26** (0.97 g, 1.65 mmol) in a 47% yield, as an oil, after silica gel column chromatography purification. R_F = 0.70 (10% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 6H, H_{Ar} Trt), 7.30 – 7.24 (m, 6H, H_{Ar} Trt), 7.22 – 7.19 (m, 3H, H_{Ar} Trt), 7.18 – 7.16 (m, 1H, H-thio), 6.97 (dq, *J* = 3.0, 1.0 Hz, 1H, H thio), 6.94 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 3.59 (t, *J* = 7.0 Hz, 2H, H_2-2), 3.41 (t, *J* = 6.5 Hz, 2H, H_2-5), 3.05 (t, *J* = 6.6 Hz, 2H, H_2-1), 2.92 – 2.84 (m, 2H, H_2-1), 1.64 (p, *J* = 6.8 Hz, 2H, H_2-2), 1.55 (dq, *J* = 8.7, 6.5 Hz, 2H, H_2-4), 1.47 – 1.36 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C_q Trt), 128.8 (CH Trt), 128.0 (CH thio), 127.8 (CH Trt), 126.9 (CH Trt), 125.2 (CH thio), 121.1 (CH thio), 114.6 (C_q thio), 86.4 (C_q Trt), 71.1 (C-2), 71.0 (C-5), 63.6 (C-1), 30.8 (C-1), 29.9 (C-2), 29.6 (C-4), 23.0 (C-3). IR/cm^{-1}: 3524, 3086, 3057, 2934, 2862, 1738, 1717, 1489, 1447, 1387, 1364, 1242, 1159, 1113, 1069, 1034.

5-(2-Methyl-1-propyloxy)-1-pentanol (27):



Compound **16** (3.56 mmol) was subjected to the general procedure B to provide **27** (0.33 g, 2.07 mmol) in a yield of 73%, as an oil, after silica gel column chromatography purification. R_F = 0.24 (20% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (t, *J* = 6.6 Hz, 2H, H_2-1), 3.31 (t, *J* = 6.5 Hz, 2H, H_2-5), 3.07 (d, *J* = 6.8 Hz, 2H, H_2-6), 1.78 – 1.72 (m, 1H, H-7), 1.53 – 1.43 (m, 4H, H_2-2, H_2-4), 1.37 – 1.27 (m, 2H, H_2-3), 0.81 (s, 3H, H_3-8), 0.79 (s, 3H, H_3-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8 (C-6), 70.8 (C-5), 62.1 (C-1), 32.3 (C-2), 29.3 (C-4), 28.2 (C-7), 22.3 (C-3), 19.3 (C-8, C-9). IR/cm^{-1}: 3335, 2934, 2859, 1470, 1383, 1366, 1115, 1055, 1007.

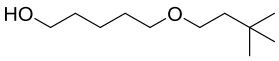
5-(3,3-Dimethyl-2-butoxy)-1-pentanol (28):



Compound **17**(2.21 mmol) was subjected to the general procedure B to provide **28** (0.2089 g, 1.11 mmol) in a 50% yield, as an oil, after silica gel column chromatography purification. R_F = 0.32 (20% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.6 Hz, 2H, H_2-1), 3.57 (dt, *J* = 9.2, 6.1 Hz, 1H, H-5a), 3.26 (dt, *J* = 9.2, 6.6 Hz, 1H, H-5b), 2.95 (q, *J* = 6.3 Hz, 1H, H-6), 1.64 – 1.51 (m, 4H, H_2-2, H_2-4), 1.50 – 1.36 (m, 2H, H_2-3), 1.03 (d, *J* = 6.3 Hz, 3H, H_3-7), 0.87 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C

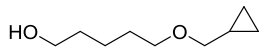
NMR (100 MHz, $CDCl_3$) δ 83.4 (C-6), 69.8 (C-5), 62.8 (C-1), 35.1 (C-8), 32.5 (C-2), 29.8 (C-4), 26.0 (C-9, C-10, C-11), 22.5 (C-3), 14.0 (C-7). IR/cm^{-1}: 3296, 2938, 2866, 1474, 1456, 1388, 1371, 1339, 1209, 1099, 1057.

5-(3,3-Dimethyl-1-butoxy)-1-pentanol (29):



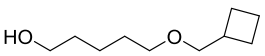
Compound **18** (2.36 mmol) was subjected to the general procedure B to provide **29** (0.2142 g, 1.14 mmol) in a yield of 48%, as an oil, after silica gel column chromatography purification. R_F = 0.22 (20% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.5 Hz, 2H, H_2-1), 3.51 – 3.36 (m, 4H, H_2-5, H_2-2), 1.60 (dq, *J* = 14.6, 6.6 Hz, 4H, H_2-2, H_2-4), 1.54 – 1.49 (m, 2H, H_2-1), 1.48 – 1.37 (m, 2H, H_2-3), 0.92 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9 (C-6), 68.2 (C-5), 62.6 (C-1), 42.9 (C-1), 32.4 (C-2), 29.7 (C-9, C-10, C-11), 29.6 (C-8), 29.5 (C-4), 22.5 (C-3). IR/cm^{-1}: 3345, 2938, 2864, 1472, 1364, 1244, 1194, 1113, 1055.

5-(Cyclopropylmethoxy)-1-pentanol (30):



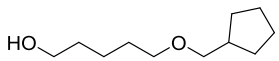
Compound **19** (2.49 mmol) was subjected to the general procedure B to provide **30** (0.19 g, 1.19 mmol) in a yield of 48%, as an oil, after silica gel column chromatography purification. R_F = 0.27 (30% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.5 Hz, 2H, H_2-1), 3.45 (t, *J* = 6.6 Hz, 2H, H_2-5), 3.25 (d, *J* = 6.9 Hz, 2H, H_2-6), 1.61 (m, 4H, H_2-2, H_2-4), 1.49 – 1.36 (m, 2H, H_2-3), 1.12 – 0.98 (m, 1H, H-7), 0.59 – 0.47 (m, 4H, H_2-8, H_2-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6 (C-6), 70.6 (C-5), 62.5 (C-1) 32.4 (C-2), 29.4 (C-4), 22.4 (C-3), 10.6 (C-7), 3.0 (C-8, C-9). IR/cm^{-1}: 3348, 2934, 2858, 1456, 1382, 1339, 1107, 1051.

5-(Cyclobutylmethoxy)-1-pentanol (31):



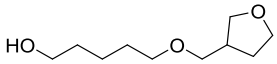
Compound **20** (1.91 mmol) was subjected to the general procedure B to provide **31** (0.18 g, 1.02 mmol) in a yield of 53%, as an oil, after silica gel column chromatography purification. R_F = 0.41 (30% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.6 Hz, 2H, H_2-1), 3.42 (t, *J* = 6.5 Hz, 2H, H_2-5), 3.27 (d, *J* = 7.2 Hz, 2H, H_2-6), 2.17 – 2.13 (m, 1H, H-7), 1.81 – 1.68 (m, 1H, H-8a), 1.64 – 1.50 (m, 7H, H_2-2, H_2-4, H_2-10, H-8b), 1.47 – 1.37 (m, 2H, H_2-3), 1.26 – 1.15 (m, 2H, H_2-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6 (C-6), 70.9 (C-5), 62.4 (C-1), 39.3 (C-7), 32.4 (C-2), 29.6 (C-8, C-10), 29.3 (C-4), 25.4 (C-9), 22.4 (C-3). IR/cm^{-1}: 3360, 2933, 2858, 1456, 1364, 1113, 1057.

5-(Cyclopentylmethoxy)-1-pentanol (32):



Compound **21** (3.02 mmol) was subjected to the general procedure B to provide **32** (0.27 g, 1.43 mmol) in a yield of 47%, as an oil, after silica gel column chromatography purification. R_F = 0.45 (30% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.5 Hz, 2H, H_2-1), 3.45 – 3.37 (m, 4H, H_2-5, H_2-6), 2.56 (p, *J* = 7.5 Hz, 1H, H-7), 2.11 – 2.00 (m, 2H, H_2-8), 1.97 – 1.79 (m, 2H, H_2-11), 1.77 – 1.65 (m, 2H, H_2-9), 1.64 – 1.54 (m, 4H, H_2-2, H_2-4), 1.46 – 1.37 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.7 (C-6), 70.9 (C-5), 62.6 (C-1), 35.1 (C-7), 32.4 (C-2), 29.7 (C-8, C-11)29.3 (C-4), 25.2 (C-9, C-10), 22.4 (C-3). IR/cm^{-1}: 3333, 2939, 2862, 1456, 1373, 1361, 1115, 1057.

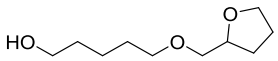
5-(*R*/*S*-Tetrahydrofuran-3-ylmethoxy)-1-pentanol (33):



Compound **22** (3.56 mmol) was subjected to the general procedure B to provide **33** (0.48 g, 2.56 mmol) in a yield of 72%, as an oil, after silica gel column chromatography purification. R_F = 0.33 (1:2, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 – 3.78 (m, 2H, H-8a,H-9a), 3.72 (dt, *J* = 8.4, 7.2 Hz, 1H, H-8b), 3.65 – 3.52 (m, 3H, H_2-1, H-9b), 3.47 – 3.27 (m, 4H, H_2-5, H_2-6), 2.58 – 2.45 (m, 1H, H-7), 2.06 – 1.94 (m, 1H, H-10a), 1.66 – 1.51 (m, 5H, H_2-2, H_2-4, H-10b), 1.47 – 1.35 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8 (C-6), 71.0 (C-5), 70.9 (C-8), 67.6 (C-9), 62.3 (C-1), 39.1 (C-7),

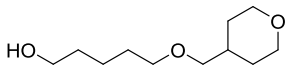
32.4 (C-2), 29.3 (C-4), 29.0 (C-10), 22.4 (C-3). IR/cm^{-1}: 3385, 2934, 2858, 1456, 1375, 1211, 1113, 1072, 1056.

5-(*R*/*S*-Tetrahydrofuran-1-ylmethoxy)-1-pentanol (34):



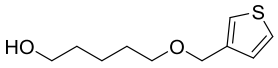
Compound **23** (2.46 mmol) was subjected to the general procedure B to provide **34** (0.35 g, 1.86 mmol) in a yield of 76%, as an oil, after silica gel column chromatography purification. R_F = 0.28 (1:2, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (ddd, *J* = 12.4, 6.9, 5.2 Hz, 1H, H-7), 3.87 (dt, *J* = 8.3, 6.6 Hz, 1H, H-10a), 3.81 – 3.71 (m, 1H, H-10b), 3.61 (t, *J* = 6.5 Hz, 2H, H_2-1), 3.48 (td, *J* = 6.6, 2.2 Hz, 2H, H_2-5), 3.44 – 3.39 (m, 2H, H_2-6), 2.02 – 1.79 (m, 3H, H_2-9, H-8a), 1.66 – 1.54 (m, 5H, H_2-2, H_2-4, H-8b), 1.48 – 1.36 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8 (C-7), 73.4 (C-6), 71.4 (C-5), 68.2 (C-10), 62.3 (C-1), 32.4 (C-2), 29.3 (C-4), 28.0 (C-9), 25.5 (C-8), 22.3 (C-3). IR/cm^{-1}: 3410, 2934, 2858, 1645, 1454, 1375, 1109, 1072, 1055.

5-(Tetrahydro-2H-pyran-4-ylmethoxy)-1-pentanol (35):



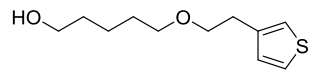
Compound **24** (1.78 mmol) was subjected to the general procedure B to provide **35** (0.14 g, 0.697 mmol) in a yield of 39%, as an oil, after silica gel column chromatography purification. R_F = 0.31 (1:2, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (m, 2H, H-9a, 10a), 3.60 (t, *J* = 6.6 Hz, 2H, H_2-1), 3.45 – 3.34 (m, 4H, H_2-5, H-9b, H-10b), 3.25 (d, *J* = 6.6 Hz, 2H, H_2-6), 1.83 (t, *J* = 3.4 Hz, 1H, H-7), 1.70 – 1.51 (m, 6H, H_2-2,H_2-4, H-8a, H-11a), 1.46 – 1.36 (m, 2H, H_2-3), 1.36 – 1.21 (m, 2H, H-8b, H-11b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.9 (C-6), 71.0 (C-5), 67.6 (C-9, C-10), 62.3 (C-1), 35.3 (C-7), 32.4 (C-2), 29.9 (C-8, C-11), 29.3 (C-4), 22.4 (C-3). IR/cm^{-1}: 3445, 2931, 2851, 1437, 1364, 1236, 1117, 1092, 1012.

5-(Thiophen-3-methoxy)-1-pentanol (36):



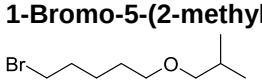
Compound **25** (2.13 mmol) was subjected to the general procedure B to provide **36** (0.23 g, 1.15 mmol) in a yield of 69%, as an oil, after silica gel column chromatography purification. R_F = 0.27 (30% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 4.9, 3.0 Hz, 1H, H thio), 7.19 (ddt, *J* = 2.1, 1.5, 0.9 Hz, 1H, H thio), 7.06 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 4.49 (s, 2H, H_2-6), 3.57 (t, *J* = 6.6 Hz, 2H, H_2-1), 3.46 (t, *J* = 6.5 Hz, 2H, H_2-5), 1.66 – 1.57 (m, 2H, H_2-4), 1.57 – 1.50 (m, 2H, H_2-2), 1.45 – 1.36 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (C_q thio), 127.3 (CH thio), 125.9 (CH thio), 122.7 (CH thio), 70.2 (C-5), 68.1 (C-6), 62.4 (C-1), 32.4 (C-2), 29.4 (C-4), 22.4 (C-3).

5-(Thiophen-3-ethoxy)-1-pentanol (37):



Compound **26** (1.65 mmol) was subjected to the general procedure B to provide **37** (0.3318 g, 1.55 mmol) in a 73% yield, as an oil, after silica gel column chromatography purification. R_F = 0.30 (30% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.9, 3.0 Hz, 1H, H thio), 7.01 (dq, *J* = 3.0, 1.0 Hz, 1H, H thio), 6.97 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 3.62 (m,4H, H_2-6, H_2-7), 3.45 (t, *J* = 6.5 Hz, 2H, H_2-5), 2.90 (td, *J* = 7.0, 0.8 Hz, 2H, H_2-1), 1.65 – 1.52 (m, 4H, H_2-2, H_2-4), 1.45 – 1.35 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.28 (C_q thio), 128.5 (CH thio), 125.2 (CH thio), 121.1 (CH thio), 71.0 (C-7), 70.9 (C-5), 62.6 (C-6), 32.4 (C-4), 30.7 (C-1), 29.4 (C-2), 22.4 (C-3). IR/cm^{-1}: 3360, 2934, 2860, 1456, 1418, 1348, 1250, 1225, 1155, 1094, 1053.

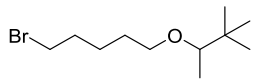
1-Bromo-5-(2-methyl-1-propyloxy)pentane (38):



Alcohol **27** (2.07 mmol) was subjected to the general procedure C to provide **38** (0.24 g, 1.08 mmol) in a yield of 52% after silica gel column chromatography purification. R_F = 0.71 (100% toluene) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (t, *J* = 6.9 Hz, 2H, H_2-5). 3.40 (t, *J* = 6.3 Hz, 2H, H_2-1), 3.16 (d, *J* = 6.7 Hz, 2H, H_2-6), 1.90 – 1.85 (m, 3H, H_2-2, H-7), 1.65 – 1.56 (m, 2H, H_2-4), 1.56 – 1.47 (m, 2H, H_2-3), 0.92 (s, 3H, H_3-8), 0.89(s, 3H, H_3-

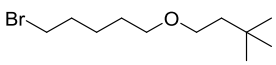
9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.9 (C-6), 70.6 (C-5), 33.7 (C-1), 32.6 (C-2), 28.9 (C-4), 28.4 (C-7), 25.0 (C-3), 19.4 (C-8, C-9). IR/cm^{-1}: 2940, 2863, 1473, 1363, 1332, 1100.

1-Bromo-5-(3,3-dimethyl-2-butoxy)pentane (39):



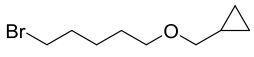
Alcohol **28** (1.11 mmol) was subjected to the general procedure C to provide **39** (0.25 g, 0.99 mmol) in a yield of 89% after silica gel column chromatography purification. R_F = 0.71 (1:1, PE:toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (dt, *J* = 9.5, 5.8 Hz, 1H, H-5a), 3.41 (t, *J* = 6.9 Hz, 2H, H_2-1), 3.24 (dt, *J* = 9.5, 6.1 Hz, 1H, H-5b), 2.94 (q, *J* = 6.3 Hz, 1H, H-6), 1.88 (p, *J* = 7.0 Hz, 2H, H_2-2), 1.64 – 1.44 (m, 4H, H_2-3, H_2-4), 1.03 (d, *J* = 6.3 Hz, 3H, H_3-7), 0.87 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3 (C-6), 69.3 (C-5), 35.1 (C-8), 33.8 (C-1), 32.7 (C-2), 29.3 (C-4), 26.0 (C-9, C-10, C-11), 25.1 (C-3), 13.9 (C-7). IR/cm^{-1}: 2938, 2866, 1477, 1369, 1335, 1099.

1-Bromo-5-(3,3-dimethyl-1-butoxy)pentane (40):



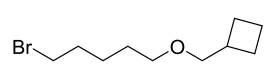
Alcohol **29** (1.14 mmol) was subjected to the general procedure C to provide **40** (0.14 g, 0.54 mmol) in a yield of 48% after silica gel column chromatography purification. R_F = 0.71 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 – 3.38 (m, 6H, H_2-1, H_2-5, H_2-6), 1.96 – 1.84 (m, 2H, H_2-7), 1.67 – 1.56 (m, 2H, H_2-2), 1.59 – 1.40 (m, 4H, H_2-3, H_2-4), 0.93 (s, 9H, H_3-9, H_3-10, H_3-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.6 (C-6), 68.2 (C-5), 43.0 (C-7), 33.7 (C-1), 32.7 (C-2), 29.8 (C-9, C-10, C-11), 29.6 (C-8), 29.0 (C-4), 25.0 (C-3). IR/cm^{-1}: 2951, 2862, 1734, 1486, 1364, 1111.

1-Bromo-5-(cyclopropylmethoxy)pentane (41):



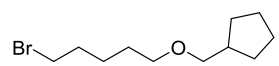
Alcohol **30** (1.19 mmol) was subjected to the general procedure C to provide **41** (0.12 g, 0.54 mmol) in a yield of 46% after silica gel column chromatography purification. R_F = 0.52 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (t, *J* = 6.4 Hz, 2H, H_2-5), 3.42 (t, *J* = 6.8 Hz, 2H, H_2-1), 3.25 (d, *J* = 6.9 Hz, 2H, H_2-6), 1.89 (dt, *J* = 14.8, 7.0 Hz, 2H, H_2-2), 1.67 – 1.56 (m, 2H, H_2-4), 1.58 – 1.47 (m, 2H, H_2-3), 1.13 – 0.98 (m, 1H, H-7), 0.58 – 0.49 (m, 2H, H_2-8), 0.20 (dt, *J* = 6.1, 4.5 Hz, 2H, H_2-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6 (C-6), 70.3 (C-5), 33.8 (C-1), 32.6 (C-2), 28.9 (C-4), 24.9 (C-3), 10.6 (C-7), 3.0 (C-8, C-9). IR/cm^{-1}: 2934, 2857, 1732, 1456, 1381, 1337, 1250, 1107, 1016.

1-Bromo-5-(cyclobutylmethoxy)pentane (42):



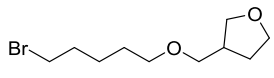
Alcohol **31** (1.02 mmol) was subjected to the general procedure C to provide **42** (0.1276 g, 0.54 mmol) in a yield of 53% after silica gel column chromatography purification. R_F = 0.67 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41, (t, *J* = 6.7 Hz, 2H, H_2-5), 3.41 (t, *J* = 6.9 Hz, 2H, H_2-1), 3.38 (d, *J* = 6.8 Hz, 2H, H_2-6), 2.60 – 2.54 (m, 1H, H-7), 2.14 – 2.01 (m, 2H, H_2-8), 1.97 – 1.81 (m, 4H, H_2-2, H_2-10), 1.80 – 1.67 (m, 2H, H_2-9), 1.66 – 1.56 (m, 2H, H_2-4), 1.56 – 1.45 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6 (C-6), 70.7 (C-5), 35.2 (C-7), 33.8 (C-1), 32.6 (C-2), 28.9 (C-4), 25.2 (C-8, C-10), 24.9 (C-3), 18.6 (C-9). IR/cm^{-1}: 2932, 2855, 1732, 1456, 1364, 1246, 1111.

1-Bromo-5-(cyclopentylmethoxy)pentane (43):



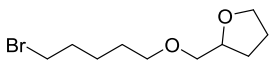
Alcohol **32** (1.43 mmol) was subjected to the general procedure C to provide **43** (0.25 g, 1.01 mmol) in a yield of 71% after silica gel column chromatography purification. R_F = 0.71 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 6.7, 6.0 Hz, 2H, H_2-5), 3.43 (t, *J* = 6.8 Hz, 1H, H_2-1), 3.27 (d, *J* = 7.1 Hz, 2H, H_2-6), 2.17 – 2.11 (m, 1H, H-7), 1.89 (dt, *J* = 14.1, 7.0 Hz, 2H, H_2-2), 1.79 – 1.66 (m, 2H, H_2-8), 1.64 – 1.45 (m, 8H, H_2-3, H_2-4, H_2-11, H_2-9), 1.29 – 1.16 (m, 2H, H_2-10). ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6 (C-6), 70.6 (C-5), 39.5 (C-7), 33.8 (C-1), 32.6 (C-2), 29.6 (C-8, C-11), 28.9 (C-4), 25.4 (C-9, C-10), 25.0 (C-3). IR/cm^{-1}: 2940, 2857, 1734, 1452, 1366, 1250, 1111.

1-Bromo-5-(*R*/*S*-tetrahydrofuran-3-ylmethoxy)pentane (44):



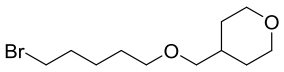
Alcohol **33** (1.86 mmol) was subjected to the general procedure C to provide **44** (0.58 g, 2.32 mmol) in a yield of 91% after silica gel column chromatography purification. R_F = 0.33 (5% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.78 (m, 2H, H-8a, H-9a), 3.78 – 3.66 (m, 1H, H-8b), 3.56 (dd, *J* = 8.7, 5.4 Hz, 1H, H-9b), 3.46 – 3.25 (m, 6H, H_2-1, H_2-5, H_2-6), 2.54 – 2.48 (m, 1H, H-7), 2.06 – 1.94 (m, 1H, H-10a), 1.92 – 1.83 (m, 2H, H_2-2), 1.65 – 1.54 (m, 3H, H_2-4, H-10b), 1.54 – 1.45 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.0 (C-6), 71.0 (C-9), 70.8 (C-5), 67.7 (C-8), 39.2 (C-7), 33.7 (C-1), 32.6 (C-2), 29.1 (C-10), 28.8 (C-4), 24.9 (C-3). IR/cm^{-1}: 2934, 2857, 1486, 1111, 1076.

1-Bromo-5-(*R*/*S*-tetrahydrofuran-1-ylmethoxy)pentane (45):



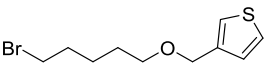
Alcohol **34** (1.86 mmol) was subjected to the general procedure C to provide **45** (0.33 g, 1.30 mmol) in a yield of 70% after silica gel column chromatography purification. R_F = 0.33 (5% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (m, 1H, H-7), 3.88 (m, 1H, H-10a), 3.75 (m, 1H, H-10b), 3.49 (m, 2H, H_2-5), 3.47-3.39 (m, 4H, H_2-1, H_2-6), 1.99 – 1.83 (m, 5H, H_2-2. H-8a , H_2-9), 1.66-1.62 (m, 3H, H-8b, H_2-4), 1.61-1.53 (m, 2H, H_2-3). ^{13}C NMR (400 MHz, $CDCl_3$) δ 77.9 (C-7), 73.6 (C-6), 71.2 (C-5), 68.3 (C-10), 33.8 (C-1), 32.6 (C-2), 28.8 (C-4), 28.1 (C-8), 25.6 (C-9), 24.9 (C-3). IR/cm^{-1}: 2938, 2860, 1456, 1437, 1117, 1070.

1-Bromo-5-(tetrahydro-2H-pyran-4-ylmethoxy)pentane (46):



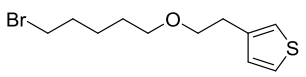
Alcohol **35** (0.31 mmol) was subjected to the general procedure C to provide **46** (0.061 g, 0.23 mmol) in a 33% yield after silica gel column chromatography purification. R_F = 0.35 (5% EtOAc in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 – 3.94 (m, 2H, H-9a, H-10a), 3.45 – 3.35 (m, 6H, H_2-1, H_2-5, H-9b, H-10b), 3.25 (d, *J* = 6.6 Hz, 2H, H_2-6), 1.93 – 1.77 (m, 3H, H_2-2, H-7), 1.68 – 1.55 (m, 4H, H_2-4, H-8a, H-11a), 1.55 – 1.46 (m, 2H, H_2-3), 1.42 – 1.19 (m, 2H, H-8b, H-11b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.0 (C-6), 70.8 (C-5), 67.8 (C-9, C-10), 35.5 (C-7), 33.8 (C-1), 32.6 (C-2), 30.0 (C-8, C-11), 28.9 (C-4), 24.9 (C-3). IR/cm^{-1}: 2924, 2845, 1734, 1384, 1115, 1092.

1-Bromo-5-(thiophen-3-methoxy)pentane (47):



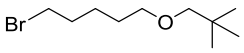
Alcohol **36** (1.15 mmol) was subjected to the general procedure C to provide **47** (0.19 g, 0.74 mmol) in a yield of 45% after silica gel column chromatography purification. R_F = 0.67 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H, H thio), 7.23 (dd, *J* = 2.9, 1.2 Hz, 1H, H thio), 7.10 (dd, *J* = 5.0, 1.2 Hz, 1H, H thio), 4.56 – 4.51 (s, 2H, H_2-6), 3.50 (t, *J* = 6.3 Hz, 2H, H_2-5), 3.44 (t, *J* = 6.8 Hz, 2H, H_2-1), 1.90 (p, *J* = 7.0 Hz, 2H, H_2-2), 1.72 – 1.59 (m, 2H, H_2-4), 1.62 – 1.48 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7 (C_q thio), 127.3 (CH thio), 126.0 (CH thio), 122.6 (CH thio), 70.0 (C-6), 68.2 (C-5), 33.8 (C-1), 32.6 (C-2), 28.9 (C-4), 25.0 (C-3). IR/cm^{-1}: 3000, 2934, 2857, 1732, 1153, 1096.

1-Bromo-5-(thiophen-3-ethoxy)pentane (48):



Alcohol **37** (1.55 mmol) was subjected to the general procedure C to provide **48** (0.28 g, 0.99 mmol) in a yield of 46% after silica gel column chromatography purification. R_F = 0.67 (100% toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 1H, H thio), 7.02 – 6.98 (m, 1H, H thio), 6.97 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 3.62 (t, *J* = 7.0 Hz, 2H, H_2-6), 3.44 (t, *J* = 6.3 Hz, 2H, H_2-5), 3.39 (t, *J* = 6.8 Hz, 2H, H_2-1), 2.90 (td, *J* = 7.0, 0.8 Hz, 2H, H_2-7), 1.92 – 1.79 (m, 2H, H_2-2), 1.64 – 1.54 (m, 2H, H_2-4), 1.53 – 1.44 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (C_q thio), 128.5 (CH thio), 125.2 (CH thio), 121.1 (CH thio), 71.1 (C-6), 70.6 (C-5), 33.9 (C-1), 32.6 (C-2), 30.8 (C-7), 28.9 (C-4), 25.0 (C-3). IR/cm^{-1}: 3102, 2934, 2857, 1734, 1109.

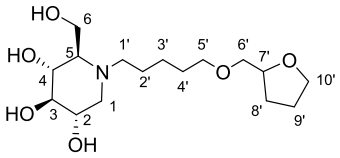
1-Bromo-5-(2,2-dimethyl-1-propoxy) pentane (66):



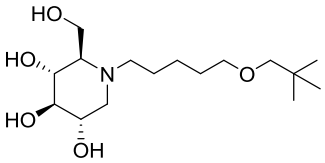
68 (2.72 g, 11.46 mmol) was synthesized from corresponding alcohol (2.70 g, 15.49 mmol) according to the general procedure C in a yield of 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (t, *J* = 6.8 Hz, 2H, H_2-1), 3.41 (t, *J* = 6.2 Hz, 2H, H_2-5), 3.04 (s, 2H, H_2-6), 1.91 – 1.87 (m, 2H, H_2-2), 1.67 – 1.42 (m, 4H, H_2-4, H_2-3), 0.90 (s, 9H, H_3-8, H_3-9, H_3-10). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6 (C-6), 71.3 (C-5), 34.1 (C-1), 32.8 (C-2), 28.9 (C-5), 26.9 (C-8, C-9, C-10), 25.1 (C-3). IR/cm^{-1}: 2941, 2863, 1473, 1363, 1331, 1102.

Synthesis of the alkylated iminosugars

***Figure 8**: Proton and carbon NMR numbering of iminosugars (**4**, **5**, **49** - **65**)*

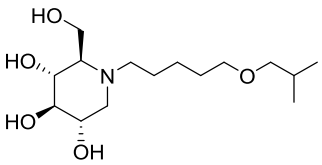


***N*-[5-(3,3-Dimethyl-1-propyloxy)pentyl]-1-deoxynojirimycin (4):**



Bromide **66** (0.30 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **4** (30 mg, 0.094 mmol, yield 77%). ^{1}H NMR (400 MHz, MeOD) δ 4.01 (dd, *J* = 12.3, 2.0 Hz, 1H, H-6a), 3.89 (dd, *J* = 12.3, 3.0 Hz, 1H, H-6b), 3.62 (ddd, *J* = 10.8, 9.2, 4.9 Hz, 1H, H-2), 3.52 (t, *J* = 9.6 Hz, 1H, H-4), 3.44 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.32 – 3.24 (m, 2H, H-3, H-1a), 3.17 (td, *J* = 12.1, 11.5, 5.5 Hz, 1H, H-1'a), 3.08 (s, 2H, H_2-6'), 3.00 (td, *J* = 12.7, 12.0, 5.4 Hz, 1H, H-1'b), 2.78 – 2.70 (m, 1H, H-1b), 2.72 (t, *J* = 11.4 Hz, 1H, H-5), 1.69 – 1.65 (m, 4H, H_2-2', H_2-4'), 1.44 (ddd, *J* = 17.2, 9.0, 5.9 Hz, 2H, H_2-3'), 0.91 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.5 (C-6'), 79.0 (C-3), 72.1 (C-5'), 69.9 (C-4), 68.8 (C-2), 67.4 (C-5), 56.5 (C-6), 55.7 (C-1), 54.0 (C-1'), 32.9 (C-7'), 30.4 (C-4'), 27.1 (C-8', C-9', C-10'), 24.8 (C-3'), 24.4 (C-2'). IR/cm^{-1}: 3284, 2347, 2326, 1018. HRMS: found 320.2431 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.2432.

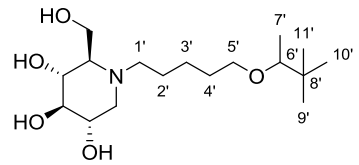
***N*-[5-(2-Methyl-1-propyloxy)pentyl]-1-deoxynojirimycin (49):**



Bromide **38** (0.30 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **49** (28 mg, 0.092 mmol, yield 46%). ^{1}H NMR (400 MHz, MeOD) δ 4.07 (d, *J* = 12.4 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.5, 2.9 Hz, 1H, H-6b), 3.67 (td, *J* = 10.1, 4.5 Hz, 1H, H-2), 3.58 (t, *J* = 9.6 Hz, 1H, H-4), 3.47 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.43 – 3.24 (m, 3H, H-1a, H-3, H-1'a), 3.22 (d, *J* = 6.6 Hz, 2H, H_2-6'), 3.10 (br s, 1H, H-1'b), 2.92 – 2.74 (m, 2H, H-5, H-1b), 1.89 – 1.81 (m, 1H, H-7'), 1.80 – 1.72 (m, 2H, H_2-2'), 1.71 – 1.62 (m, 2H, H_2-4'), 1.54 – 1.41 (m, 2H, H_2-3'), 0.93 (d, *J* = 6.7 Hz, 6H, H_3-8', H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 77.6 (C-6'), 77.2 (C-3), 70.2 (C-5'), 68.1 (C-4), 67.0 (C-2), 66.1 (C-5), 55.5 (C-6), 54.0 (C-1), 52.6 (C-1'), 28.9 (C-4'), 28.2 (C-7'), 23.3 (C-3'), 22.9 (C-2'), 18.3 (C-8', C-9'). $[\alpha]^{20}_D$ = -7.17 (c = 0.56, MeOH). IR/cm^{-1}: 3333, 2871, 1670, 1432, 1383, 1201, 1131, 1031. HRMS: found 306.22757 $[C_{15}H_{31}NO_5+H]^+$, calculated for $[C_{15}H_{31}NO_5+H]^+$ 306.22750.

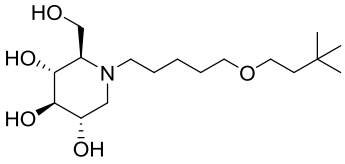
***N*-[5-(3,3-Dimethyl-2-butoxy)pentyl]-1-deoxynojirimycin (50):**

Bromide **39** (0.32 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **50** (31 mg, 0.094 mmol, yield 47%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 12.4 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.6, 2.7 Hz, 1H, H-6b), 3.72 (td, *J* = 10.4, 4.9 Hz, 1H, H-2),



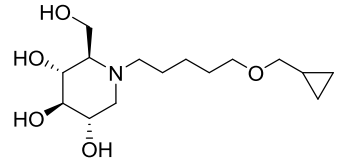
3.68 – 3.58 (m, 3H, H-3, H-4, H-5'a), 3.48 (dd, *J* = 12.0, 4.9 Hz, 1H, H-1a), 3.43 – 3.35 (m, 3H, H-1'a, H-3, H-5'b), 3.22 (td, *J* = 12.2, 5.1 Hz, 1H, H-1'b), 3.07 (br d, *J* = 9.8 Hz, 1H, H-5), 3.03 (d, *J* = 6.3 Hz, 1H, H-6'), 3.01 (dd, *J* = 12.5, 10.9 Hz, 1H, H-1b), 1.81 (dt, *J* = 11.1, 5.7 Hz, 2H, H_2-2'), 1.65 (dt, *J* = 8.8, 5.8 Hz, 2H, H_2-4'), 1.57 – 1.44 (m, 2H, H_2-3'), 1.07 (d, *J* = 6.3 Hz, 3H, H_3-7'), 0.90 (s, 9H, H_3-9', H_3-10', H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 83.3 (C-6'), 76.7 (C-3), 68.9 (C-5'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.5 (C-1), 52.9 (C-1'), 34.6 (C-8'), 29.3 (C-4'), 25.0 (C-9', C-10', C-11'), 23.2 (C-3'), 22.6 (C-2'), 12.8 (C-7'). $[\alpha]^{20}_D$ = -6.94 (c = 0.63, MeOH). IR/cm^{-1}: 3330, 2956, 2875, 1672, 1439, 1203, 1134, 1029. HRMS: found 334.25885 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

N-[5-(3,3-Dimethyl-1-butoxy)pentyl]-1-deoxynojirimycin (51):



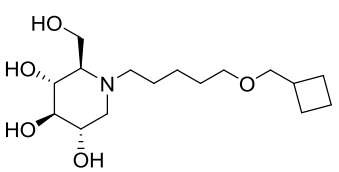
Bromide **40** (0.299 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **51** (28 mg, 0.085 mmol, yield 43%). ^{1}H NMR (400 MHz, MeOD) δ 4.12 (d, *J* = 12.5 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.3, 2.8 Hz, 1H, H-6b), 3.71 (td, *J* = 10.4, 10.0, 4.4 Hz, 1H, H-2), 3.62 (t, *J* = 9.7 Hz, 1H, H-4), 3.50 (t, *J* = 7.3 Hz, 2H, H_2-6'), 3.50 (dd, *J* = 9.0, 1.5 Hz, 1H, H-1a), 3.46 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.43 – 3.36 (m, 2H, H-3, H-1'a), 3.22 (td, *J* = 12.1, 5.2 Hz, 1H, H-1b), 3.07 (br d, *J* = 10.3 Hz, 1H, H-5), 3.00 (t, *J* = 11.7 Hz, 1H, H-1b), 1.90 – 1.71 (m, 2H, H_2-2'), 1.65 (ddd, *J* = 13.7, 7.5, 6.0 Hz, 2H, H_2-4'), 1.51 (t, *J* = 7.4 Hz, 2H, H_2-7'), 1.53 – 1.43 (m, 2H, H_2-3'), 0.94 (s, 9H, H_3-9', H_3-10', H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 70.0 (C-5'), 67.9 (C-6'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.4 (C-6), 53.3 (C-1), 52.9 (C-1'), 42.6 (C-7'), 29.7 (C-4), 28.7 (C-9', C-10', C-11'), 25.8 (C-3), 25.0 (C-2), 22.6 (C-8'). $[\alpha]^{20}_D$ = +0.56 (c = 0.57, MeOH). IR/cm^{-1}: 3343, 2954, 2870, 1673, 1433, 1203, 1134. HRMS: found 334.25886 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

N-[5-(Cyclopropylmethoxy)pentyl]-1-deoxynojirimycin (52):



Bromide **41** (0.30 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **52** (30 mg, 0.097 mmol, yield 49%). ^{1}H NMR (400 MHz, MeOD) δ 4.13 (d, *J* = 12.6 Hz, 1H, H-6a), 3.94 (dd, *J* = 12.7, 3.1 Hz, 1H, H-6b), 3.73 (td, *J* = 10.3, 4.7 Hz, 1H, H-2), 3.64 (t, *J* = 9.8 Hz, 1H, H-4), 3.52 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.51 – 3.46 (m, 1H, H-1a), 3.40 (t, *J* = 9.2 Hz, 1H, H-3), 3.40 – 3.36 (m, 1H, H-1'a), 3.30 (d, *J* = 6.9 Hz, 2H, H_2-6'), 3.23 (td, *J* = 12.3, 5.3 Hz, 1H, H-1'b), 3.08 (br d, *J* = 10.1 Hz, 1H, H-5), 3.01 (t, *J* = 11.7 Hz, 1H, H-1b), 1.91 – 1.73 (m, 2H, H_2-2'), 1.72 – 1.63 (m, 2H, H_2-4'), 1.55 – 1.45 (m, 2H, H_2-3'), 1.10 – 1.00 (m, 1H, H-7'), 0.57 – 0.51 (m, 2H, H_2-8'), 0.22 (dt, *J* = 6.1, 4.4 Hz, 2H, H_2-9'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 75.3 (C-6'), 69.8 (C-5'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.6 (C-6), 53.4 (C-1), 52.9 (C-1'), 28.7 (C-4'), 23.1 (C-3'), 22.5 (C-2'), 10.0 (C-7'), 2.1 (C-8', C-9'). $[\alpha]^{20}_D$ = -6.08 (c = 0.59, MeOH). IR/cm^{-1}: 3346, 2866, 1672, 1430, 1202, 1134, 1032. HRMS: found 304.21194 $[C_{15}H_{29}NO_5+H]^+$, calculated for $[C_{15}H_{29}NO_5+H]^+$ 304.21185.

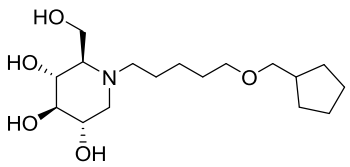
N-[5-(Cyclobutylmethoxy)pentyl]-1-deoxynojirimycin (53):



Bromide **42** (0.31 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **53** (25 mg, 0.079 mmol, yield 39%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 12.5 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.7, 3.1 Hz, 1H, H-6b), 3.71 (td, *J* = 10.7, 10.2, 4.7 Hz, 1H, H-2), 3.63 (t, *J* = 9.8 Hz, 1H, H-4), 3.49 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.48 (dd, *J* = 11.8, 5.2 Hz, 1H, H-1a), 3.43 (d, *J* = 6.8 Hz, 2H, H_2-6'), 3.43 – 3.36 (m, 1H, H-1'a), 3.39 (t, *J* = 9.4 Hz, 1H, H-3),

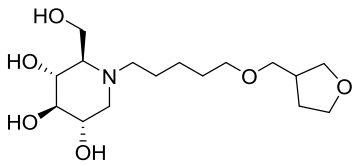
3.22 (td, *J* = 12.3, 5.3 Hz, 1H, H-1'b), 3.06 (br d, *J* = 11.2 Hz, 1H, H-5), 3.01 (t, *J* = 11.7 Hz, 1H, H-1b), 2.63 – 2.53 (m, 1H, H-7'), 2.14 – 2.03 (m, 2H, H_2-8'), 2.03 – 1.91 (m, 2H, H_2-10'), 1.91 – 1.72 (m, 4H, H_2-2', H_2-9'), 1.67 (ddd, *J* = 13.7, 7.5, 5.9 Hz, 2H, H_2-4'), 1.51 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 75.2 (C-6'), 70.2 (C-5'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.4 (C-1), 52.9 (C-1'), 35.1 (C-7'), 28.7 (C-4'), 24.6 (C-8', C-9'), 23.1 (C-3'), 22.5 (C-2'), 18.0 (C-10'). $[\alpha]^{20}_D$ = -6.02 (c = 0.50, MeOH). IR/cm^{-1}: 3341, 2938, 2865, 1673, 1431, 1202, 1135, 1031. HRMS: found 318.22761 $[C_{16}H_{31}NO_5+H]^+$, calculated for $[C_{16}H_{31}NO_5+H]^+$ 318.22750.

N-[5-(Cyclopentylmethoxy)pentyl]-1-deoxynojirimycin (54):



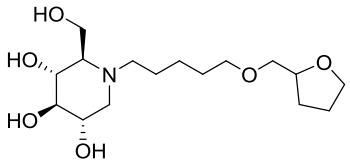
Bromide **43** (0.30 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **54** (23 mg, 0.069 mmol, yield 35%). ^{1}H NMR (400 MHz, MeOD) δ 4.13 (d, *J* = 12.5 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.6, 3.1 Hz, 1H, H-6b), 3.72 (dt, *J* = 14.7, 4.6 Hz, 1H, H-2), 3.63 (t, *J* = 9.7 Hz, 1H, H-4), 3.52 – 3.44 (m, 1H, H-1a), 3.49 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.43 – 3.35 (m, 2H, H-3, H-1'a), 3.33 (d, *J* = 7.1 Hz, 2H, H_2-6'), 3.22 (td, *J* = 12.3, 5.3 Hz, 1H, H-1'b), 3.07 (d, *J* = 9.5 Hz, 1H, H-5), 3.00 (t, *J* = 11.7 Hz, 1H, H-1b), 2.21 – 2.12 (m, 1H, H-7'), 1.88 – 1.71 (m, 4H, H_2-2', H_2-8'), 1.71 – 1.54 (m, 6H, H_2-9', H_2-10', H_2-4'), 1.51 – 1.48 (m, 2H, H_2-3'), 1.35 – 1.22 (m, 2H, H_2-11'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 75.3 (C-6'), 70.1 (C-5'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.5 (C-1), 52.8 (C-1'), 39.3 (C-7'), 29.2 (C-8', C-11'), 28.7 (C-9', C-10'), 25.0 (C-4'), 23.1 (C-3'), 22.7 (C-2'). $[\alpha]^{20}_D$ = -4.76 (c = 0.46, MeOH). IR/cm^{-1}: 3346, 2950, 2867, 1673, 1433, 1203, 1133, 1032. HRMS: found 332.24323 $[C_{17}H_{33}NO_5+H]^+$, calculated for $[C_{17}H_{33}NO_5+H]^+$ 332.24315.

N-[5-(*R*/*S*-Tetrahydrofuran-3-ylmethoxy)pentyl]-1-deoxynojirimycin (55):



Bromide **44** (0.29 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **55** (58.5 mg, 0.17 mmol, yield 88%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 12.6 Hz, 1H, H-6a), 3.93 (dd, *J* = 12.4, 3.0 Hz, 1H, H-6b), 3.85 (dd, *J* = 8.3, 5.5 Hz, 1H, H-9'a), 3.83 (dd, *J* = 8.7, 7.2 Hz, 1H, H-10'a), 3.78 – 3.69 (m, 2H, H-9'b, H-2), 3.63 (t, *J* = 9.8 Hz, 1H, H-4), 3.58 (dd, *J* = 8.6, 5.5 Hz, 2H, H_2-10'b), 3.52 – 3.47 (m,1H, H-1a), 3.50 (td, *J* = 6.3, 1.7 Hz, 2H, H_2-5'), 3.44 (dd, *J* = 9.2, 6.3 Hz, 1H, H-6'a), 3.43 – 3.35 (m, 3H, H-1'a, H-3, H-6'b), 3.20 – 3.18 (m, 1H, H-1'b), 3.07 (br d, *J* = 9.9 Hz, 1H, H-5), 3.01 (t, *J* = 11.7 Hz, 1H, H-1b), 2.59 – 2.48 (m, 1H, H-7'), 2.02 – 1.98 (m, 1H, H-8'a), 1.91 – 1.72 (m, 2H, H_2-2'), 1.72 – 1.60 (m, 3H, H-8'b, H_2-4'), 1.53 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 72.5 (C-6'), 70.5 (C-10'), 70.3 (C-5'), 67.4 (C-4), 67.3 (C-9'), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.5 (C-1), 52.9 (C-1'), 39.0 (C-7'), 28.7 (C-4'), 28.5 (C-8'), 23.1 (C-3'), 22.5 (C-2'). IR/cm^{-1}: 3346, 2970, 2942, 1738, 1070, 1430, 1366, 1199, 1132, 898. $[\alpha]^{20}_D$ = -1.89 (c = 1.17, MeOH). HRMS: found 334.22282 $[C_{16}H_{31}NO_6+H]^+$, calculated for $[C_{16}H_{31}NO_6+H]^+$ 334.22241.

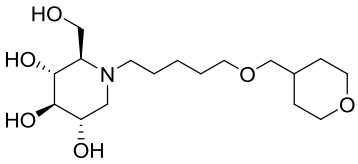
N-[5-(*R*/*S*-Tetrahydrofuran-1-ylmethoxy)pentyl]-1-deoxynojirimycin (56):



Bromide **45** (0.29 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide 5**6** (10 mg, 0.030 mmol, yield 15%). ^{1}H NMR (600 MHz, MeOD) δ 4.12 (d, *J* = 11.5 Hz, 1H, H-6a), 4.07 – 4.01 (m, 1H, H-7'), 3.91 (dd, *J* = 12.5, 3.2 Hz, 1H, H-6b), 3.85 (dt, *J* = 8.2, 6.7 Hz, 1H, H-10'a), 3.76 (td, *J* = 7.7, 6.1 Hz, 1H, H-10'b), 3.69 – 3.67 (m, 1H, H-2), 3.60 (dd, *J* = 12.7, 6.6 Hz, 1H, H-4), 3.51 (td, *J* = 6.2, 3.8 Hz, 1H, H-5'), 3.47 – 3.34 (m, 5H, H_2-6', H-1a, H-1'a, H-3), 3.20 (td, *J* = 12.4, 5.0 Hz, 1H, H-1b), 3.04 (d, *J* = 9.9 Hz, 1H, H-5), 2.99 (t, *J* = 11.7 Hz, 1H, H-1'b), 2.01 – 1.95 (m, 1H, H-8'a), 1.94 – 1.87 (m, 1H, H-9'), 1.87 – 1.71 (m, 2H,

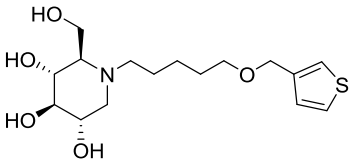
H_2-2'), 1.66 (tt, *J* = 7.5, 5.9 Hz, 2H, H_2-4'), 1.63 – 1.57 (m, 1H, H-8'b), 1.54 – 1.43 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 79.4 (C-7'), 78.2 (C-3), 74.6 (C-6'), 72.0 (C-5'), 69.2 (C-10'), 68.8 (C-5), 67.8 (C-4), 67.4 (C-2), 54.9 (C-1), 54.8 (C-6), 54.3 (C-1'), 29.9 (C-4'), 28.9 (C-8'), 26.6 (C-9'), 24.5 (C-3'), 23.9 (C-2'). IR/cm^{-1}: 3367, 2964, 2902, 1674, 1396, 1066. $[\alpha]^{20}_D$ = -9.8 (c = 0.20, MeOH). HRMS: found 334.22266 $[C_{16}H_{31}NO_6+H]^+$, calculated for $[C_{16}H_{31}NO_6+H]^+$ 334.22241.

N-[5-(Tetrahydro-2H-pyran-4-ylmethoxy)pentyl]-1-deoxynojirimycin (57):



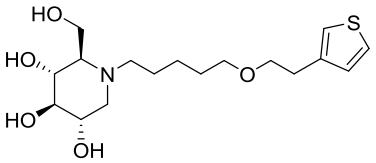
Bromide **46** (0.29 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **57** (35 mg, 0.10 mmol, yield 50%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 12.5 Hz, 1H, H-6a), 3.92 (dd, *J* = 11.8, 2.6 Hz, 1H, H-6b), 3.99 – 3.94 (m, 2H, H-9'a, H-10'a), 3.70 (ddd, *J* = 11.2, 9.3, 4.9 Hz, 1H, H-2), 3.62 (dd, *J* = 10.4, 9.2 Hz, 1H, H-4), 3.49 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.48 – 3.35 (m, 5H, H-9'b, H-10'b, H-1a, H-1'a, H-3), 3.31 (d, *J* = 6.4 Hz, 2H, H_2-6'), 3.23 (dd, *J* = 12.1, 5.3 Hz, 1H, H-1'b), 3.06 (dd, *J* = 10.3, 2.7 Hz, 1H, H-5), 3.01(t, *J* = 11.7 Hz, 1H, H-1b), 1.92 – 1.84 (m, 1H, H-7'), 1.84 – 1.72 (m, 2H, H_2-2'), 1.72 – 1.62 (m, 4H, H_2-4', H-8'a, H-11'a), 1.57 – 1.45 (m, 2H, H_2-3'), 1.34 – 1.32 (m, 2H, H-8'b, H-11'b). ^{13}C NMR (100 MHz, MeOD) δ 76.8 (C-3), 75.5 (C-6'), 70.2 (C-5'), 67.3 (C-9', C-10'), 67.3 (C-4), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.4 (C-1), 52.8 (C-1'), 35.2 (C-7'), 29.6 (C-8', C-11'), 28.7 (C-4'), 23.1 (C-3'), 22.5 (C-2'). $[\alpha]^{20}_D$ = -4.01 (c = 0.70, MeOH). IR/cm^{-1}: 3333, 2923, 2859, 1671, 1433, 1387, 1200, 1136, 1088, 1032. HRMS: found 348.23809 $[C_{17}H_{33}NO_6+H]^+$, calculated for $[C_{17}H_{33}NO_6+H]^+$ 348.23806.

N-[5-(Thiophen-3-methoxy)pentyl]-1-deoxynojirimycin (58):



Bromide **47** (0.29 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **58** (41 mg, 0.12 mmol, yield 59%). ^{1}H NMR (400 MHz, MeOD) δ 7.41 (dd, *J* = 5.0, 3.0 Hz, 1H, H thio), 7.34 – 7.31 (m, 1H, H thio), 7.10 (dd, *J* = 5.0, 1.2 Hz, 1H, H thio), 4.54 (s, 2H, H_2-6'), 4.12 (d, *J* = 12.2 Hz, 1H, H-6a), 3.92 (dd, *J* = 12.7, 3.1 Hz, 1H, H-6b), 3.71 (td, *J* = 10.1, 4.5 Hz, 1H, H-2), 3.62 (t, *J* = 9.8 Hz, 1H, H-4), 3.54 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.46 (dd, *J* = 12.1, 4.8 Hz, 1H, H-1a), 3.43 – 3.36 (m, 2H, H-1'a, H-3), 3.21 (td, *J* = 12.3, 5.2 Hz, 1H, H-1'b), 3.11 – 3.02 (m, 1H, H-5), 2.99 (t, *J* = 11.7 Hz, 1H, H-1b), 1.89 – 1.74 (m, 2H, H_2-2'), 1.69 (ddd, *J* = 13.6, 7.5, 6.0 Hz, 2H, H_2-4'), 1.53 – 1.45 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.5, 127.1, 125.6, 122.6 (C-thio), 76.7 (C-3), 69.3 (C-5'), 67.6 (C-6'), 67.4 (C-4), 66.4 (C-2), 66.0 (C-5), 53.5 (C-6), 53.5 (C-1), 52.9 (C-1'), 28.6 (C-4'), 23.1 (C-3'), 22.5 (C-2'). $[\alpha]^{20}_D$ = -3.16 (c = 0.82, MeOH). IR/cm^{-1}: 3346, 2963, 2867, 1672, 1429, 1366, 1202, 1133, 1032. HRMS: found 346.16843 $[C_{16}H_{27}NO_5S+H]^+$, calculated for $[C_{16}H_{27}NO_5S+H]^+$ 346.16837.

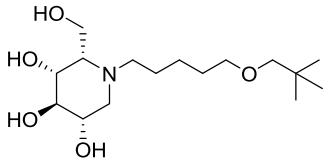
N-[5-(Thiophen-3-ethoxy)pentyl]-1-deoxynojirimycin (59):



Bromide **48** (0.29 mmol) was subjected to the general procedure D with 1-deoxynojirimycin (0.20 mmol) to provide **59** (10 mg, 0.028 mmol, yield 14%). ^{1}H NMR (400 MHz, MeOD) δ 7.33 (dd, *J* = 5.0, 2.9 Hz, 1H, H thio), 7.11 (dd, *J* = 3.0, 1.1 Hz, 1H, H thio), 7.02 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 4.12 (d, *J* = 12.5 Hz, 1H, H-6a), 3.92 (d, *J* = 12.3 Hz, 1H, H-6b), 3.74 – 3.70 (m, 1H, H-2), 3.68 (t, *J* = 6.7 Hz, 2H, H_2-6'), 3.62 (t, *J* = 9.7 Hz, 1H, H-4), 3.52 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.45 (dd, *J* = 12.1, 4.8 Hz, 1H, H-1a), 3.42 – 3.34 (m, 2H, H-3, H-1'a), 3.23 – 3.13 (m, 1H, H-1'b), 3.06 – 3.00 (m, 1H, H-5), 2.97 (t, *J* = 11.7 Hz, 1H, H-1b), 2.91 (dd, *J* = 7.1, 6.3 Hz, 2H, H_2-7'), 1.86 – 1.70 (m, 2H, H_2-2'), 1.70 – 1.62 (m, 2H, H_2-4'), 1.52 – 1.40 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.3, 128.1, 124.7, 120.7 (C thio), 76.8 (C-3), 70.8 (C-6'), 69.9 (C-5'), 67.5 (C-4), 66.4 (C-2), 66.0 (C-5), 53.4 (C-1), 53.0 (C-1'), 30.2 (C-7'), 28.7 (C-4'), 24.0 (C-3'),

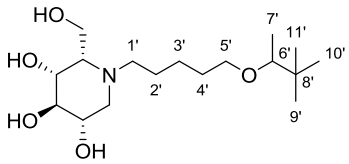
23.1 (C-2'). $[\alpha]^{20}_D$ = -9.09 (c = 0.20, MeOH). IR/cm^{-1}: 3358, 3018, 2943, 2870, 1736, 1677, 1439, 1366, 1205, 1134, 1031. HRMS: found 360.18495 $[C_{17}H_{29}NO_5S+H]^+$, calculated for $[C_{17}H_{29}NO_5S+H]^+$ 360.18392.

_N_-[5-(3,3-Dimethyl-1-propyloxy)pentyl]-1-L-_ido_-1-deoxynojirimycin (5):



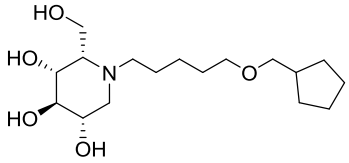
Bromide **66** (0.30 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **5** (16 mg, 0.049 mmol, yield 40%). ^{1}H NMR (400 MHz, MeOD) δ 4.05 (br s, 1H, H-3), 4.03 – 3.94 (m, 3H, H_2-6, H-2), 3.71 – 3.64 (m, 1H, H-4), 3.56 (t, *J* = 7.0 Hz, 1H, H-5), 3.43 (t, *J* = 6.3 Hz, 1H, H-2), 3.27 – 3.18 (m, 2H, H-5'), 3.07 (s, 2H, H_2-6'), 3.10 – 2.87 (m, 4H, H_2-1, H_2-1'), 1.82 – 1.53 (m, 4H, H_2-2', H_2-4'), 1.51 – 1.37 (m, 2H, H_2-3'), 0.90 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (100 MHz, MeOD) δ 82.4 (C-6'), 72.4 (C-3), 72.3 (C-5'), 70.3 (C-4), 64.0 (C-2), 55.8 (C-6), 55.3 (C-1'), 53.3 (C-1), 32.9 (C-7'), 30.4 (C-4'), 26.7 (C-8', C-9', C-10'), 24.8 (C-2'), 13.3 (C-3'). IR/cm^{-1}: 3369, 2935, 2860, 1066. HRMS: found 320.2431 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.2432.

_N_-[5-(3,3-Dimethyl-2-butoxy)pentyl]-L-_ido_-1-deoxynojirimycin (60):



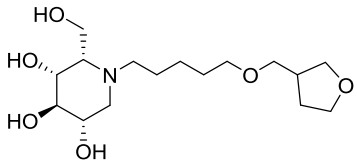
Bromide **39** (0.32 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **60** (14 mg, 0.042 mmol, yield 21%). ^{1}H NMR (400 MHz, MeOD) δ 4.05 (br s, 1H, H-3), 4.03 – 3.95 (m, 3H, H_2-6, H-2), 3.93 – 3.86 (m, 1H, H-4), 3.64 (ddd, *J* = 8.9, 7.6, 4.7 Hz, 1H, H-5'a), 3.58 – 3.47 (m, 2H, H-1a, H-5), 3.41 – 3.30 (m, 4H, H-1a, H_2-1', H-5'b), 3.04 (q, *J* = 6.3 Hz, 1H, H-6'), 1.95 – 1.72 (m, 2H, H_2-2'), 1.66 (dt, *J* = 12.9, 6.2 Hz, 2H, H_2-4'), 1.56 – 1.44 (m, 2H, H_2-3'), 1.08 (d, *J* = 6.4 Hz, 3H, H_3-7'), 0.91 (s, 9H, H_3-9', H_3-10', H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 83.3 (C-6'), 70.9 (C-3), 68.9 (C-5'), 67.5 (C-2), 66.6 (C-4), 62.4 (C-5), 60.0 (C-6), 53.7 (C-1'), 53.0 (C-1), 34.6 (C-8'), 29.4 (C-4'), 25.0 (C-9', C-10', C-11'), 23.3 (C-3'), 22.0 (C-2'), 12.8 (C-7'). IR/cm^{-1}: 3372, 2972, 1673, 1393, 1203, 1139, 1066. $[\alpha]^{20}_D$ = +1.44 (c = 0.28, MeOH). HRMS: found 334.25937 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

_N_-[5-(Cyclopentylmethoxy)pentyl]-L-_ido_-1-deoxynojirimycin (61):



Bromide **43** (0.30 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **61** (23 mg, 0.069 mmol, yield 35%). ^{1}H NMR (400 MHz, MeOD) δ 4.05 (br s, 1H, H-3), 4.03 – 3.94 (m, 3H, H_2-6, H-2), 3.90 (br s, 1H, H-4), 3.60 – 3.51 (m, 2H, H-1a, H-5), 3.49 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.40 – 3.33 (m, 5H, H-1b, H_2-1', H_2-6'), 2.17 (dt, *J* = 14.9, 7.6 Hz, 1H, H-7'), 1.96 – 1.72 (m, 4H, H_2-2', H-8'a, H-11'a), 1.71 – 1.54 (m, 6H, H_2-9', H_2-10', H_2-4'), 1.48 (p, *J* = 7.7 Hz, 2H, H_2-3'), 1.34 – 1.25 (m, 2H, H_2-11'). ^{13}C NMR (100 MHz, MeOD) δ 75.3 (C-6'), 70.9 (C-3), 70.2 (C-5'), 67.5 (C-2), 66.6 (C-4), 62.4 (C-5), 60.0 (C-6), 53.6 (C-1'), 53.0 (C-1), 39.3 (C-7'), 29.2 (C-8', C-11'), 28.7 (C-9', C-10'), 25.0 (C-4'), 23.1 (C-3'), 21.9 (C-2'). IR/cm^{-1}: 3374, 2953, 2873, 1678, 1440, 1205, 1136, 1072. $[\alpha]^{20}_D$ = +4.33 (c = 0.46, MeOH). HRMS: found 332.24355 $[C_{17}H_{33}NO_5+H]^+$, calculated for $[C_{17}H_{33}NO_5+H]^+$ 332.24315.

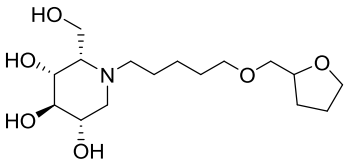
_N_-[5-(_R_/_S_-Tetrahydrofuran-3-ylmethoxy)pentyl]-L-_ido_-1-deoxynojirimycin (62):



Bromide **44** (0.29 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **62** (20 mg, 0.060 mmol, yield 30%). ^{1}H NMR (400 MHz, MeOD) δ 4.08 – 3.95 (m, 4H, H_2-6, H-3, H-2), 3.90 (t, *J* = 3.0 Hz, 1H, H-4), 3.88 – 3.80 (m, 2H. H-9'a, H-10'a), 3.77 – 3.70

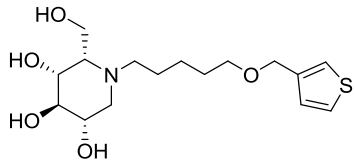
(m, 1H, H-9'b), 3.58 (dd, *J* = 8.6, 5.5 Hz, 1H, H-10'b), 3.56 – 3.52 (m, 2H, H-5, H-1a), 3.50 (td, *J* = 6.3, 1.8 Hz, 2H, H_2-5'), 3.44 (dd, *J* = 9.3, 6.2 Hz, 1H, H-6'), 3.41 – 3.32 (m, 4H, H-1b, H_2-1', H-6'b), 2.59 – 2.49 (m, 1H, H-7'), 2.09 – 1.99 (m, 2H, H_2-8'), 1.97 – 1.72 (m, 2H, H_2-2'), 1.71 – 1.60 (m, 2H, H_2-4'), 1.48 (p, *J* = 7.6 Hz, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 72.5 (C-6'), 70.9 (C-3), 70.5 (C-10'), 70.3 (C-5'), 67.5 (C-2), 67.3 (C-9'), 66.7 (C-4), 62.4 (C-5), 60.0 (C-6), 53.7 (C-1'), 53.0 (C-1), 39.0 (C-7'), 28.7 (C-4'), 28.5 (C-8'), 23.1 (C-3'), 21.9 (C-2'). IR/cm^{-1}: 3355, 2971, 1674, 1201, 1132, 1066. $[\alpha]^{20}_D$ = +10.50 (c = 0.40, MeOH). HRMS: found 334.22299 $[C_{16}H_{31}NO_6+H]^+$, calculated for $[C_{16}H_{31}NO_6+H]^+$ 334.22241.

N-[5-(*R*/*S*-Tetrahydrofuran-1-ylmethoxy)pentyl]-L-*ido*-1-deoxynojirimycin (63):



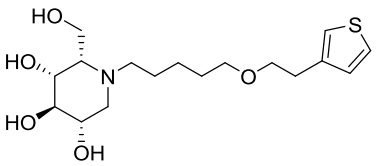
Bromide **45** (0.29 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **63** (23 mg, 0.069 mmol, yield 34%). ^{1}H NMR (400 MHz, MeOD) δ 4.12 – 3.94 (m, 5H, H-3, H-7', H-2, H_2-6), 3.93 – 3.83 (m, 2H, H-4, H-10'a), 3.82 – 3.74 (m, 1H, H-10'b), 3.58 – 3.48 (m, 5H, H-1a, H-5, H_2-5', H-6'a), 3.48 – 3.29 (m, 3H, H-1b, H_2-1'), 2.08 – 1.85 (m, 4H, H-8'a, H_2-9', H-2'a), 1.85 – 1.73 (m, 1H, H-2'b), 1.70 – 1.59 (m, 3H, H_2-4', H-8'b), 1.50 (q, *J* = 7.5 Hz, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 78.0 (C-3), 73.1 (C-6'), 70.9 (C-7'), 70.6 (C-5'), 67.8(C-10'), 67.6 (C-2), 66.7 (C-4), 62.4 (C-5), 59.9 (C-6), 53.7 (C-1'), 53.0 (C-1), 28.6 (C-4'), 27.5 (C-8'), 25.2 (C-9'), 23.1 (C-3'), 21.8 (C-2'). IR/cm^{-1}: 3346, 2871, 1673, 1432, 1200, 1132, 1071. $[\alpha]^{20}_D$ = +12.5 (c = 0.46, MeOH). HRMS: found 334.22280 $[C_{16}H_{31}NO_6+H]^+$, calculated for $[C_{16}H_{31}NO_6+H]^+$ 334.22241.

N-[5-(Thiophen-3-methoxy)pentyl]-L-*ido*-1-deoxynojirimycin (64):



Bromide **47** (0.29 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **64** (14 mg, 0.042 mmol, yield 21%). ^{1}H NMR (400 MHz, MeOD) δ 4.54 (d, *J* = 0.7 Hz, 2H, H_2-6'), 4.04 (br s, 1H, H-3), 4.01 – 3.93 (m, 3H, H_2-6, H-2), 3.89 (t, *J* = 3.7 Hz, 1H, H-4), 3.54 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.55 – 3.44 (m, 2H, H-1a, H-5), 3.39 – 3.28 (m, 3H, H-1b, H_2-1'), 1.98 – 1.72 (m, 2H, H_2-2'), 1.69 (dt, *J* = 8.3, 6.3 Hz, 2H, H_2-4'), 1.50 (q, *J* = 7.6 Hz, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.5(C_q thio), 127.1 , 125.6, 122.6 (CH thio), 70.9 (C-3), 69.3 (C-5'), 67.6 (C-6'), 67.5 (C-2), 66.6 (C-4), 62.4 (C-5), 60.0 (C-6), 53.6 (C-1'), 53.0 (C-1), 28.7 (C-4), 23.1 (C-2), 21.8 (C-3). IR/cm^{-1}: 3346, 2970, 1673, 1409, 1201, 1133, 1066. $[\alpha]^{20}_D$ = +8.28 (c = 0.29, MeOH). HRMS: found 346.16823 $[C_{16}H_{27}NO_5S$ +H]$^+$, calculated for $[C_{16}H_{27}NO_5S+H]^+$ 346.16827.

N-[5-(Thiophen-3-ethoxy)pentyl]-L-*ido*-1-deoxynojirimycin (65):



Bromide **48** (0.29 mmol) was subjected to the general procedure D with L-*ido*-1-deoxynojirimycin (0.20 mmol) to provide **65** (36 mg, 0.099 mmol, yield 49%). ^{1}H NMR (400 MHz, MeOD) δ 7.33 (dd, *J* = 4.9, 3.0 Hz, 2H, H thio), 7.14 – 7.09 (m, 1H, H thio), 7.02 (dd, *J* = 4.9, 1.3 Hz, 1H, H thio), 4.05 (br s, 1H, H-3), 4.01 – 3.95 (m, 3H, H-2, H_2-6), 3.90 (t, *J* = 3.7 Hz, 1H, H-4), 3.68 (t, *J* = 6.7 Hz, 2H, H_2-6'), 3.56 – 3.47 (m, 2H, H-1a, H-5), 3.52 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.38 – 3.28 (m, 3H, H-1b, H_2-1'), 2.94 – 2.88 (m, 2H, H_2-7'), 1.93 – 1.70 (m, 2H, H_2-2'), 1.70 – 1.64 (m, 2H, H_2-4'), 1.53 – 1.37 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.3 (C_q thio), 128.1, 124.7, 120.7 (CH thio), 70.9 (C-3), 70.8 (C-6'), 70.0 (C-5'), 67.5 (C-2), 66.6 (C-4), 62.4 (C-5), 60.0 (C-6), 53.7 (C-1'), 53.0 (C-1), 30.2 (C-7'), 28.7 (C-4'), 23.1 (C-3'), 21.8 (C-2'). IR/cm^{-1}: 3355, 2971, 1674, 1394, 1202, 1066. $[\alpha]^{20}_D$ = +2.52 (c = 0.71, MeOH). HRMS: found 360.18397 $[C_{17}H_{29}NO_5S$ +H]$^+$, calculated for $[C_{17}H_{29}NO_5S+H]^+$ 360.18392.

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5 Biphenyl-L-*ido* DNJ Derivatives as Dual GCS/GBA2 Inhibitors

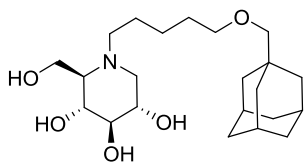
Introduction

N-alkyl-deoxynojiricin derivatives (*N*-alkyl iminosugars) are an important class of biologically active molecules that are applied both in fundamental glycobiology studies and in clinical settings.[1] *N*-alkyl-DNJ derivatives are potent inhibitors of the glucosylceramide metabolizing enzymes, glucosylceramide synthase (GCS) and neutral glucosylceramidase (GBA2) as well as intestinal glucosidases. Literature reports suggest that this dual activity make such *N*-modified DNJs promising leads for the development of type 2 diabetes. In these studies, it was also shown that *N*-alkyl derivatives of the C-5 epimer of DNJ, the L-*ido*-configured

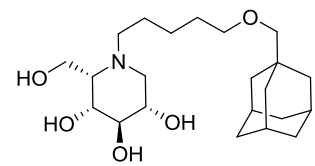
iminosugars are at least equally potent GCS and GBA2 inhibitors as their DNJ counterparts, but do not target intestinal glycosidases. Based on this comparative selectivity, L-*ido*-DNJ derivatives may be considered as starting point for the development of therapeutics for the treatment of lysosomal storage disorders, in particular those in which GCS (and possibly also GBA2) are involved, such as Gaucher disease.[2]

As is described in Chapter 4, GCS, the enzyme responsible for the biosynthesis of glucosylceramide, is targeted in substrate reduction therapy for Gaucher disease. Compensatory overexpression of GBA2 in the cytoplasm has however been associated with LSDs symptoms as well.[3] Therefore, dual GCS/GBA2 inhibitors that are otherwise clean with respect to other glycoprocessing enzymes are thought to be promising compounds for the development of new and more effective drugs for treatment of these LSDs. This in turn indicates that further perusal of diverse, *N*-alkyl-L-*ido*-DNJ derivatives is a worthy research objective.

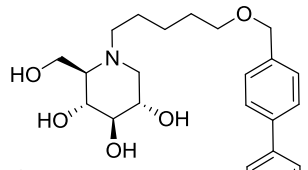
***Figure 1**: Various potent GCS and GBA2 inhibitors*



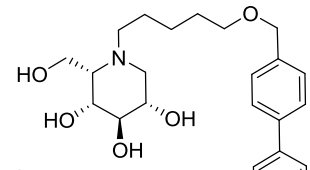
1 IC_{50} GCS 200 nM
IC_{50} GBA1 0.1 μM
IC_{50} GBA2 2 nM



2 IC_{50} GCS 100 nM
IC_{50} GBA1 30 μM
IC_{50} GBA2 1 nM



3 IC_{50} GCS 8 nM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 0.6 nM



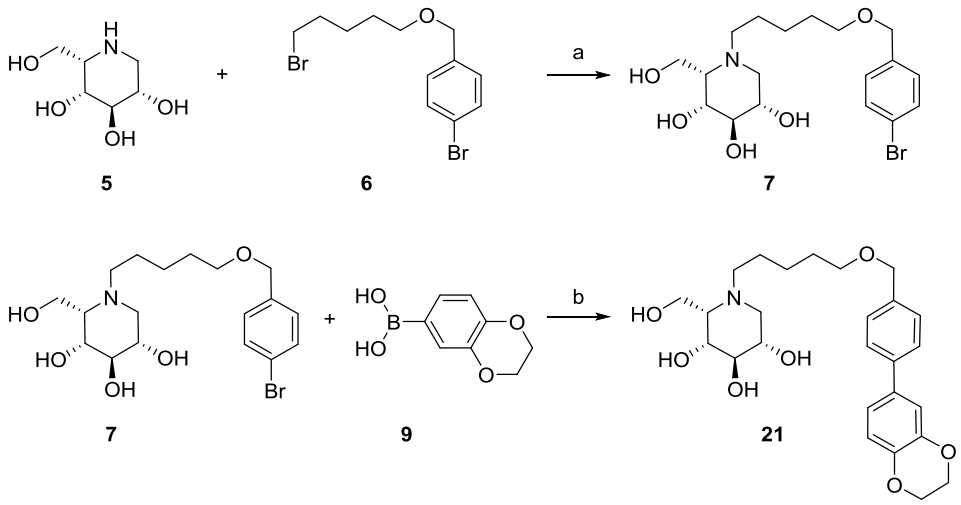
4 IC_{50} GCS 6 nM
IC_{50} GBA1 15 μM
IC_{50} GBA2 1 nM

From initial work on comparing the efficacy of DNJ and L-*ido*-DNJ derivatives as GCS/GBA2 inhibitors, *N*-AMP DNJ (MZ-21, **1**) and *N*-AMP L-*ido*-DNJ (MZ-31, **2**) emerged as the most effective compounds. Both are potent GCS/GBA2 inhibitors and, as outlined above, whereas compound **1** has a considerable number of other glycosidases as off-targets, compound **2** is much more selective. More recent studies on a series of *N*-alkyl and *N*-aryl derivatives revealed *N*-penyloxymethylbiaryl DNJ (**3**) and its L-ido-DNJ derivative (**4**) as more potent inhibitors that retain the selectivity profile of their parent compounds, **1** and **2**, respectively.[2] In these studies, the impact on altering the nature of the nitrogen substituent has been studied in depth on DNJ,

but less so on L-*ido*-DNJ, this while the latter class is considered more promising for the discovery of new LSD therapeutics.[2] For this reason, it was decided to expand the number and variety of *N*-substituted, L-idose configured iminosugars. The results on the design, synthesis and evaluation of a set of such compounds as GCS/GBA1/GBA2 inhibitors in comparison with relevant literature compounds, including their D-glucose configured counterparts, are presented in this Chapter.

Results and discussion

Scheme 1: *General approach to synthesize biphenyl substituted iminosugars*

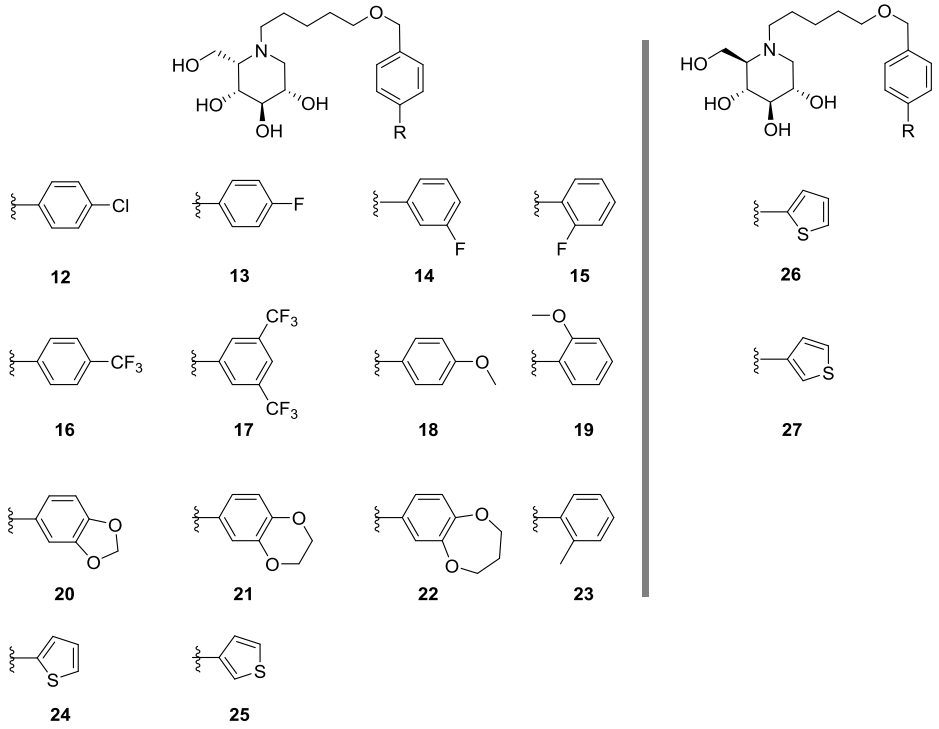


Reagents and conditions: [**a**] K_2CO_3, DMF, 80 °C, 46%; [**b**] $Pd(PPh_3)_4$, NaOMe, EtOH, 65 °C, 18 h, 11%.

The synthetic strategy employed to obtain functionalized biphenyl substituents is illustrated in Scheme 1 for the synthesis of protected catechol derivative **21**. Following this strategy, first a large batch of bromobenzyl-L-*ido*-DNJ derivative (such as the *para*-bromobenzyl derivative **7**) is made, which is then diversified into compound families using Suzuki cross-coupling methodology with a variety of commercially available phenylboronates as the cross-coupling counterpart. Thus, and following conditions as described in previous chapters,[4] L-*ido*-DNJ **5** is alkylated with bromide **6** to provide in acceptable yields and in a scalable fashion compound **7**. Treatment of bromide **7** with catechol **9**, a catalytic amount of $Pd(Ph_3)_4$ and sodium methoxide in ethanol provided after HPLC purification compound **21** in 11% yield. This yield is not impressive. Moreover, yields from the cross-coupling/purifications sequence involving different phenylboronates, yielding other library entries (see Figure 3 for their structure and in the experimental part for their synthesis) were sometimes, as low as 1%.

Nonwithstanding these yields, which were not optimized, sufficient quantities of material in excellent structural purity were obtained to perform enzyme inhibition assays, which was the primary objective of the research in this Chapter: are L-*ido*-DNJ derivatives more potent and selective than their D-*gluco*-counterparts in inhibiting GCS and GBA2 irrespective of the nature of the nitrogen substituent.

Figure 3: *Substituents for external phenyl ring modifications*



In order to obtain insight in what causes the low efficiency in the Suzuki reactions, HPLC traces were perused for potential side products that were formed during the reaction. From these studies it became apparent that compound **10** (Figure 4; when starting from DNJ) and **11** (from L-*ido*-DNJ), the dehalogenated starting materials, were formed as major products. Dehalogenation of the aryl halide is a known side reaction in Suzuki cross couplings and can be suppressed by the addition of tertiary amine bases such as trimethylamine.[5]

Figure 4: *Dehalogenated side products*

In case needed (for instance when larger quantities of a given iminosugar are required) optimization of the cross-coupling event including the addition of such amines may be considered. Alternative literature procedures for the optimization of this key step includes modulating the amount of potassium carbonate used and the temperature at which the reaction is executed.[6]

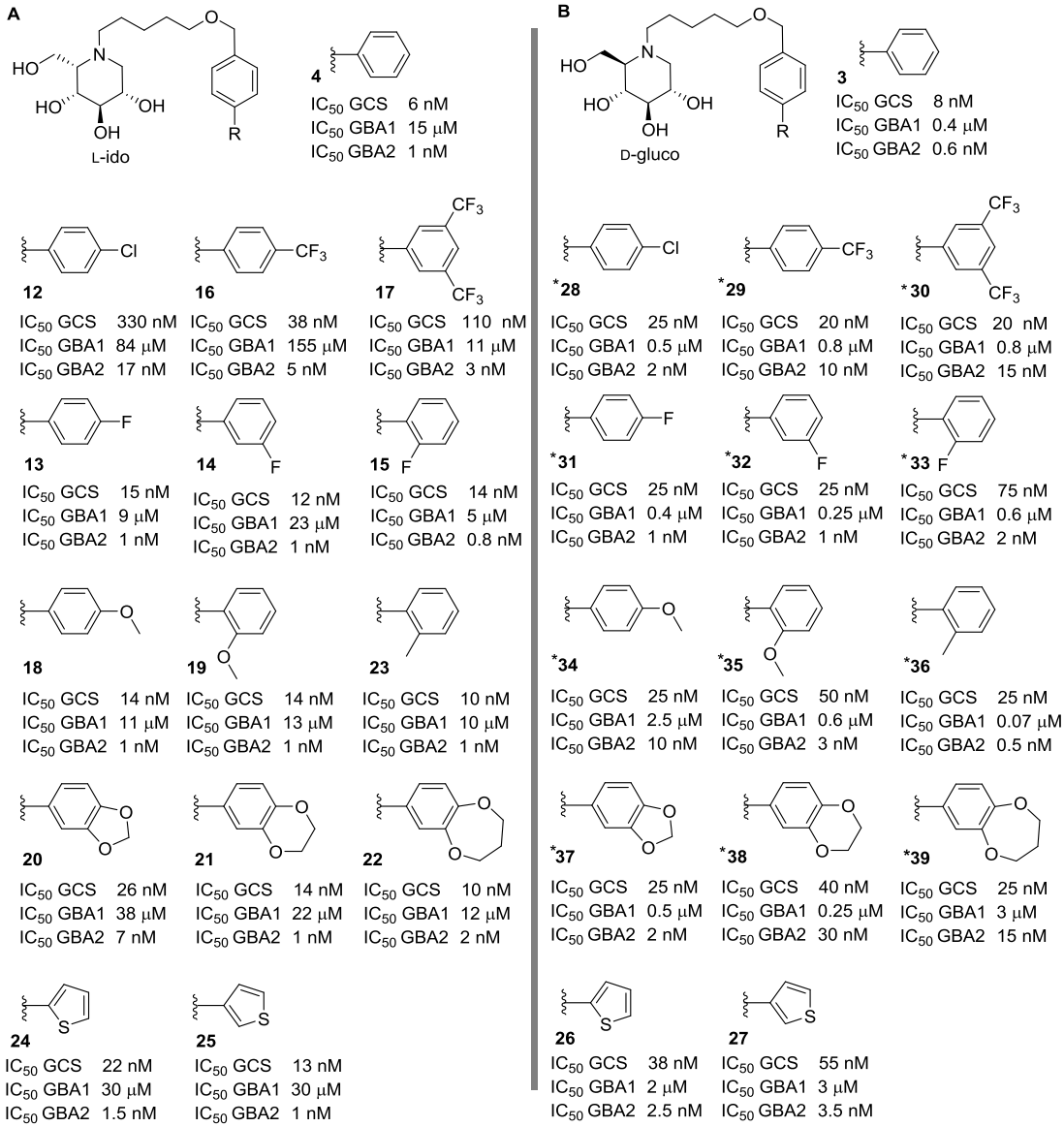
Inhibition activity

As discussed above, an established trend is that L-idose configured iminosugars are more potent GCS inhibitors than their D-glucose configured counterparts. As can be seen (Figure 5), this trend in general also holds up after evaluation of the newly synthesized DNJ derivatives. There are however some notable exceptions to this rule: compounds **12**, **16** and **17** are less potent GCS inhibitors than their corresponding DNJ derivatives (**28**, **29** and **30**). The differences in potency are however too small to draw any structure-activity relationship conclusions from this observation. It can be generally concluded that the compound series contain many nanomolar GCS inhibitors and therefore many compounds that may be of interest for further perusal as *in vivo* GCS inhibitors.

With the exception of **12** and **16** all compounds in the L-*ido* series inhibit GBA1 with IC_{50} values ranging from 5 to 40 μM. These compounds are therefore rather potent inhibitors of GBA1, however there is a considerable window between GCS and GBA1 (GCS: nanomolar, GBA1: micromolar). This window is much more pronounced than the one in the D-*gluco* series, containing many nanomolar inhibitors of GBA1 (an enzyme one does not wish to inhibit, neither in relation to type 2 diabetes nor in relation to LSDs). Finally, all compounds inhibit GBA2 in the nanomolar range (IC_{50} 0.8 – 17 nM), with *ortho*-F substituted **15** (IC_{50} = 0.8 nM) as the most potent compound of the series. Though less pronounced than seen for GCS, the L-*ido*-compounds do seem to outperform their D-*gluco* counterparts in inhibition potency towards GBA2. Returning to GCS inhibition potency, one striking observation is that *para*-fluoride **13** significantly more potent than *para*-chloride **12**. This observation is opposite from what is observed in the D-*gluco* series (compare **28** and **31**).

Besides the construction of new L-*ido*-DNJ derivatives bearing known (for DNJ) *N*-substituents the compounds synthesised in the framework of this Chapter also include a new functionality: thiophene derivatives **24**-**27** with the thiophene (appended through either of the two optional carbons) replacing the terminal phenyl ring in **3** and **4**. Following the trend L-*ido* congeners **24** and **25** are 2 to 3 times more potent GCS inhibitors than the corresponding DNJ compounds **26** and **27**, though overall GCS inhibitory potency has suffered from this phenyl-to-tiophene substitution.

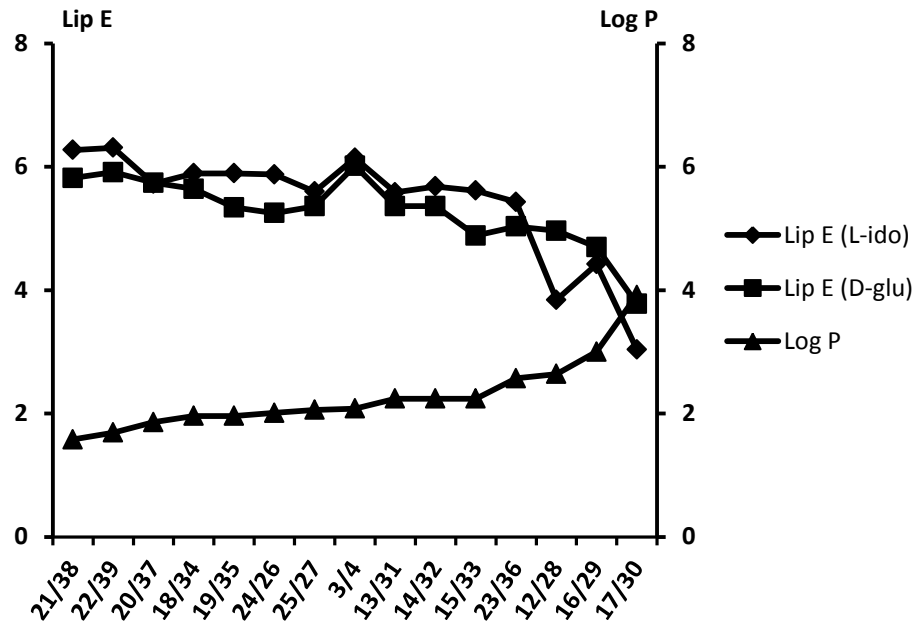
***Figure 5**: Structures and GCS, GBA1 and GBA2 IC_{50} values of the biphenyl analogue containing iminosugars*



*IC_{50} values of 29 – 40 are from the literature.[2]

Overall, the introduction of different substituents at the biphenyl external ring has not led to inhibitors with significantly improved or decreased activity against GCS, GBA1 and GBA2, compared to the lead structures. When looking at selectivity, however, *para*-CF_3 substituted compound **16** may be of interest, as it is the most selective GCS/GBA2 dual inhibitor when taking into account GBA1 as an undesired off-target.

***Figure 6**: Lipophilic ligand efficiency values (LipE) of D-gluco and L-ido series for GCS inhibition*



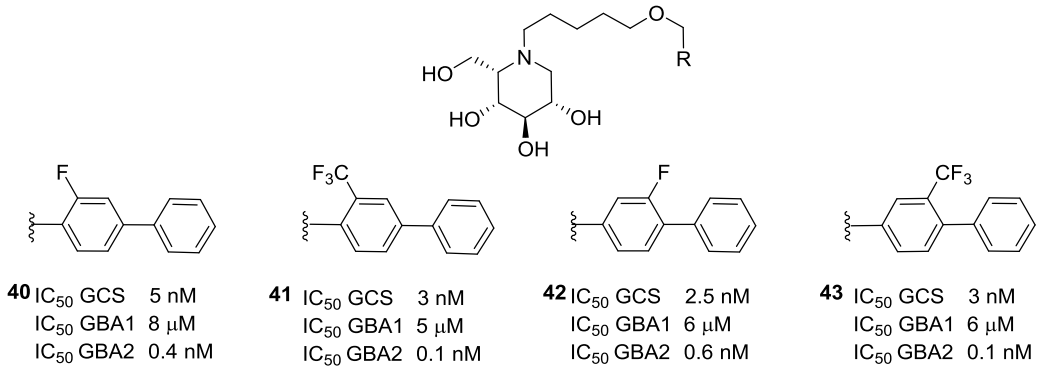
To obtain some more insight into the potential relevance of the here-presented inhibitors for potential future *in vivo* application, their lipophilic ligand efficiency (LipE) was calculated (Figure 6). LipE is defined as pIC_{50} - LogP, which is a composite parameter often referred to when correlating the potency of a molecule towards an isolated target (or gleaned from an *in vitro* assay) to its potential druglikeness.[7] A high LipE indicates the affinity of the inhibitor with the target enzyme tends to be driven by specific molecule-protein interaction, rather than a non-specific entropy-driven binding.[7] It can be observed from Figure 6 that the L-*ido* series exhibits better performance in this index when the LogP value is low, whereas the D-*glu* series has a higher LipE value when the logP value is higher (see: **12/28**, **16/29** and **17/30**). From all the iminosugars discussed in this Chapter, compounds **21** and **22** seem to perform better than lead structure **4** in this evaluation. It should however be realized that this evaluation is not very precise, as for instance chiral information is not included and furthermore that the lipophilicity data is generated *in silico*, rather than by experimentation.

Conclusion

In this Chapter, 14 new L-*ido*-DNJ derivatives were designed and synthesized, with as key step a Suzuki-Miyaura cross coupling event. The results in this Chapter complement literature studies, and while no spectacularly active and selective new inhibitors are identified, the list of

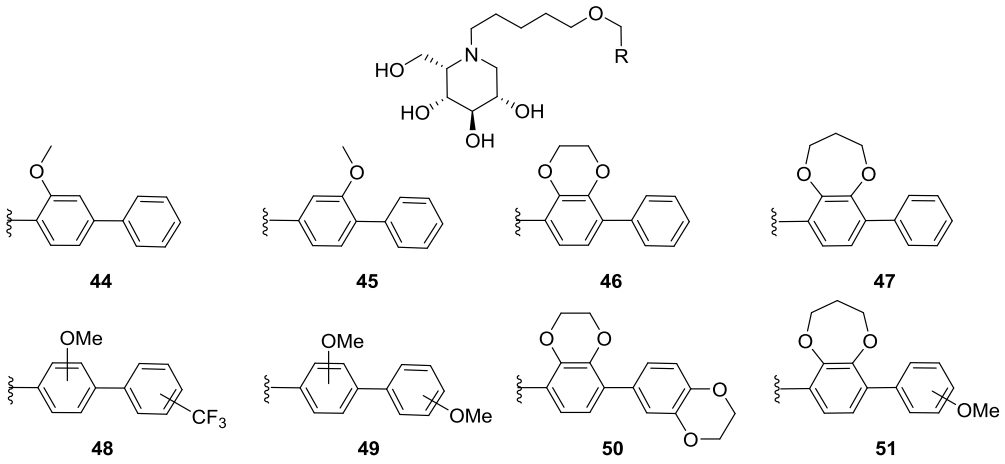
compounds with D-*gluco* and L-*ido* configuration and bearing a large number of different *N*-alkyl groups, alongside with GCS/GBA1/GBA2 inhibitory potencies obtained, now provide some hints as to what would make a *N*-substituted iminosugar a potent and/or selective GCS/GBA2 inhibitor. For instance, as can be concluded from the inhibitors presented here, alteration of the terminal phenyl ring in a biphenyl substituent does little for activity/selectivity (but is also not detrimental).

Figure 7: *Potent internal phenyl ring modified L-ido iminosugar derivatives*



This is in contrast to the literature report on related compounds, but in which focus has been more on modulating the internal phenyl ring of the biphenyl moiety. For instance, L-*ido*-DNJ derivatives **41** - **44** (Figure 7) turned out to be potent GCS/GBA2 inhibitors, more so than lead compound **4** as well as noniminosugar GCS inhibitors reported in the literature.[2] One future direction may be to take those inner-ring substituents for potency/selectivity, and equip these with the most optimal terminal rings in terms of logP values, leading to, for instance, analogues **49**–**52** in (Figure 8) as potentially interesting targets for the future.

Figure 8: *Low logP modified biphenyl L-ido iminosugars*



Experimental section

Enzyme inhibition assays: The potencies (IC_{50} values) of the *N*-alkyl-DNJ derivatives as GCS, GBA1 and GBA2 inhibitors were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[8] Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbeliferyl-β-D-glucoside as substrate.[9] Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and sodium taurocholate (0.2%, w/v). Assays were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

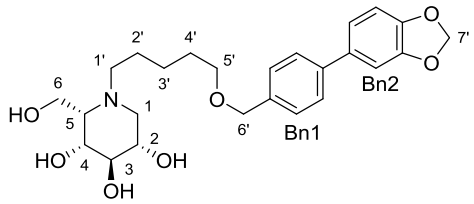
GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with 4-methylumbeliferyl-β-D-glucoside as substrate.[8] GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbeliferyl-β-D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General compound synthesis, purification and analysis methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz), Bruker 600 (600/150 MHz) or Bruker 600 (850/215 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[10] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo

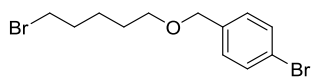
Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ = 589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer, column size d = 26 mm, l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 µm, 19 x 150 mm column).

General procedure: Suzuki-Miyaura cross coupling: Solutions and stock solutions used were degassed with ultrasonic bath with an argon flow for at least 15 minutes. The reactions were carried out under argon protection. A stock solution of *N*-[5-(4-bromobenzyloxy)pentyl]-1-deoxynojirimycin (1.2 M) in ethanol, a stock solution of boronic acid (1.5 M) in ethanol and a stock solution of $Pd(PPh_3)_4$ (5%) in ethanol were made. NaOMe (0.180 gram, 3.3 mmol) was added to the reaction vails containing an argon atmosphere, followed by the additions of the stock solutions of *N*-[5-(4-bromobenzyloxy)pentyl]-1-deoxynojirimycin (1.2 M, 0.417 mL, 0.5 mmol), boronic acid (1.5 M, 0.500 mL, 0.75 mmol) and $Pd(PPh_3)_4$ (2 mol%, 0.40mL). The reaction mixture was stirred at 65 °C for 18 h. After HPLC analysis indicated the complete consumption of starting material, the reaction mixture was diluted with ethanol filtered over Cilite and the volatiles were evaporated. The residue was purified by HPLC purification. Yields vary from 1% - 11%.

***Figure 9**: Proton and carbon NMR numbering of iminosugars:*

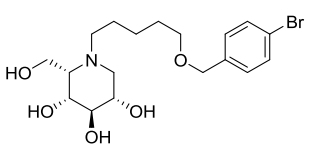


5-(4-Bromobenzyloxy)pentyl-1-bromide (6):



To a mixture of 5-(4-bromobenzyloxy)pentane-1-ol (4.00 g, 14.6 mmol) and triphenyl phosphine (5.80 g, 22.2 mmol) in DCM (150 mL) was added CBr_4 (7.35 g, 22.2 mmol) at 0 °C. The reaction mixture was stirred for 2 hours. After which TLC analysis showed the complete consumption of starting material, Celite was added and the volatiles were evaporated. The residue was purified with silica gel column (4:1 → 0:1, PE:toluene) to give **6** (3.20 g, 7.03 mmol, 50%) as yellow oil. R_F = 0.70 (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.38 (m, 2H, H_{Ar} Bn), 7.24 – 7.11 (m, 2H, H_{Ar} Bn), 4.44 (s, 2H, H_2-6), 3.46 (t, *J* = 6.3 Hz, 2H, H_2-5), 3.40 (t, *J* = 6.8 Hz, 2H, H_2-1), 1.97 – 1.80 (m, 2H, H_2-2), 1.71 – 1.58 (m, 2H, H_2-4), 1.58 – 1.43 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (C_q Bn), 131.5 (CH_{Ar} Bn), 129.3 (CH_{Ar} Bn), 121.4 (C_q Bn), 72.2 (C-6), 70.2 (C-5), 33.9 (C-1), 32.6 (C-2), 29.0 (C-4), 25.0 (C-3). IR/cm^{-1}: 2935, 2856, 1487, 1356, 1093, 1010.

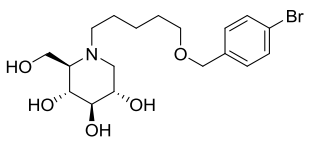
***N*-[5-(4-Bromobenzyloxy)-pentyl]-L-*ido*-1-deoxynojirimycin (7):**



To a mixture of **6** (7.57g, 22.73 mmol) and K_2CO_3 (4.27, 30.90 mmol) was added a solution of **5** (2.47g, 15.1 mmol) in DMF (75 mL). This was stirred overnight at 80 °C. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified with silica gel column (4:1 EtOAc: MeOH + 1% NH_4OH → 6:4:1 EtOH:H_2O:NH_4OH) to give **7** in 46% yield (3.22g, 7.70 mmol). ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, *J* = 8.1 Hz, 2H, H_{Ar} Bn), 7.25 (dd, *J* = 8.2, 3.5 Hz, 2H, H_{Ar} Bn),

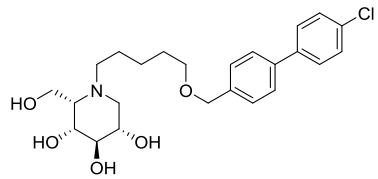
4.43 (s, 2H, H_2-6'), 3.84 (t, *J* = 5.3 Hz, 2H, H_2-6), 3.77 – 3.66 (m, 1H, H-4), 3.59 – 3.53 (m, 1H, H-2), 3.47 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.42 (t, *J* = 8.5 Hz, 1H, H-3), 3.09 – 3.05 (m, 1H, H-5), 2.83 (dd, *J* = 12.3, 4.8 Hz, 1H, H-1a), 2.80 – 2.73 (m, 1H, H-1'a), 2.71 – 2.65 (m, 1H, H-1'b), 2.61 (dd, *J* = 12.4, 9.7 Hz, 1H, H-1b), 1.80 – 1.47 (m, 4H, H_2-2', H_2-4'), 1.38 (p, *J* = 7.7 Hz, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.1 (C_q Bn), 132.4 (CH_{Ar} Bn), 130.5 (CH_{Ar} Bn), 122.2 (C_q Bn), 75.5 (C-3), 72.9 (C-6'), 72.6 (C-4), 71.4 (C-5'), 71.0 (C-2), 64.1 (C-5), 57.6 (C-6), 55.4 (C-1'), 52.8 (C-1), 30.5 (C-2'), 28.1 (C-4'), 24.9 (C-3'). $[\alpha]^{20}_D$ = 10.4 (c = 1.00, MeOH). IR/cm^{-1}: 3339, 1670, 1433, 1200, 1134, 1070. HRMS: found 418.12236, 420.12032 $[C_{18}H_{29}BrNO_5+H]^+$, calculated for $[C_{18}H_{29}BrNO_5+H]^+$ 418.12237, 420.12030.

N-[5-(4-Bromobenzyloxy)-pentyl]-1-deoxynojirimycin (8):



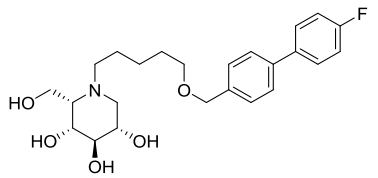
8 (3.57 g, 8.57 mmol) was synthesized from **6** (2.00 g, 12.8 mmol) and DNJ (5.16 g, 15.4 mmol) according to the procedure described for the preparation of compound **8** as a white solid with 67% yield. R_F = 0.45 (30% MeOH in EtOAc, 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.47 (m, 2H, H_{Ar} Bn), 7.33 – 7.27 (m, 2H, H_{Ar} Bn), 4.50 (s, 2H, H_2-6'), 4.09 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6a), 3.94 (dd, *J* = 12.5, 3.0 Hz, 1H, H-6b), 3.76 – 3.70 (m, 1H, H-2), 3.62 (t, *J* = 9.5 Hz, 1H, H-4), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.49 – 3.38 (m, 2H, H-1a, H-3), 3.31 – 3.25 (m, 1H, H-1'a), 3.23 – 3.14 (m, 1H, H-1'b), 3.02 (dd, *J* = 11.7, 5.2 Hz, 1H, H-5), 2.95 (t, *J* = 11.5 Hz, 1H, H-1b), 1.88 – 1.75 (m, 2H, H_2-2'), 1.73 – 1.69 (m, 2H, H_2-4'), 1.55 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 137.8 (C_q Bn), 131.1 (CH_{Ar} Bn), 129.3 (CH_{Ar} Bn), 120.9 (C_q Bn), 76.9 (C-3), 71.6 (C-6'), 69.8 (C-5'), 67.9 (C-4), 66.8 (C-2), 66.0 (C-5), 54.4 (C-6), 53.8 (C-1), 52.7 (C-1'), 28.8 (C-4'), 23.2 (C-3'), 22.8 (C-2'). $[\alpha]^{20}_D$ = -0.2 (c = 1.00, MeOH). IR/cm^{-1}: 3273, 1670, 1433, 1274, 1200, 1132, 1030, 1012. HRMS: found 418.12236, 420.12032 $[C_{18}H_{29}BrNO_5+H]^+$, calculated for $[C_{18}H_{29}BrNO_5+H]^+$ 418.12237, 420.12030.

N-[5-((4'-Chloro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (12):



12 (4.0 mg, 0.009 mmol, 2% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (600 MHz, MeOD) δ 7.65 – 7.57 (m, 4H, H_{Ar} Bn2), 7.44 (ddd, *J* = 8.2, 4.5, 2.2 Hz, 4H, H_{Ar} Bn1), 4.55 (s, 2H, H_2-6'), 4.07 – 3.88 (m, 4H, H-4, H_2-6, H-2), 3.84 (s, 1H, H-3), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.39 (m, 2H, H-5. H-1a), 3.35 – 3.23 (m, 3H, H-1b, H_2-1'), 1.98 – 1.66 (m, 4H, H_2-2', H_2-4'), 1.54 – 1.43 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 140.7, 139.4, 134.4, (C_q BiPh), 130.0, 129.5, 127.9 (C_{Ar} BiPh), 73.6 (C-6'), 72.3 (C-4), 71.0 (C-5'), 69.0 (C-2), 68.2 (C-3), 63.8 (C-5), 62.4 (C-6), 55.0 (C-1'), 54.2 (C-1), 30.2 (C-4'), 24.6 (C-3'), 24.1 (C-2'). $[\alpha]^{20}_D$ = +3.33 (c = 0.06, MeOH). IR/cm^{-1}: 3319, 2920, 2867, 1674, 1437, 1204, 1134, 1072. HRMS: found 450.20396 $[C_{24}H_{32}ClNO_5+H]^+$, calculated for $[C_{24}H_{32}ClNO_5+H]^+$ 450.20418.

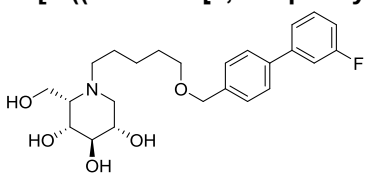
N-[5-((4'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (13):



13 (12.4 mg, 0.028 mmol, 6% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.53 (m, 4H, H_{Ar} Bn1), 7.46 – 7.37 (m, 2H, H_{Ar} Bn2), 7.23 – 7.06 (m, 2H, H_{Ar} Bn2), 4.54 (s, 2H, H_2-6'), 4.02 (s, 1H, H-4), 3.99 – 3.90 (m, 3H, H_2-6, H-2), 3.85 (t, *J* = 4.0 Hz, H-3), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.42 (m, 2H, H-5, H-1a), 3.35 – 3.30 (m, 3H, H-1b, H_2-1'), 1.96 – 1.81 (m, 1H, H-2'a), 1.73 – 1.69 (m, 3H, H-2'b, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 165.1, 162.7, 140.8, 138.9 (C_q BiPh), 129.8, 129.5, 127.9, 127.9, 116.6, 116.4, 116.4 (C_{Ar} BiPh), 73.6 (C-6), 72.3 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.0 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +5.45 (c = 0.22, MeOH). IR/cm^{-1}: 3362, 2924, 1676,

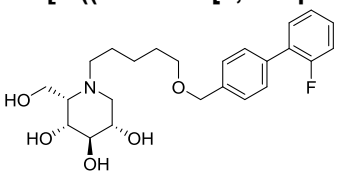
1439, 1205, 1134, 1074. HRMS: found 434.23353 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((3'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (14):



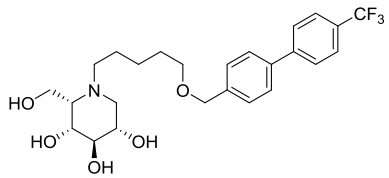
14 (7.8 mg, 0.017 mmol, 3% yield) was synthesized according the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 8.16 – 7.41 (m, 8H, H_{Ar} BiPh), 4.58 (s, 2H, H_2-6'), 4.04 (br s, 1H, H-4), 4.00 – 3.96 (m, 3H, H_2-6, H-2), 3.89 (d, *J* = 4.0 Hz, 1H, H-3), 3.59 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.56 – 3.46 (m, 2H, H-5, H-1a), 3.41 – 3.32 (m, 3H, H-1b, H_2-1'), 2.00 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.55 – 1.51 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 163.5, 143.2, 138.3 (C_q BiPh), 130.3 – 113.0 (C_{Ar} BiPh), 72.1 (C-6'), 70.9 (C-4), 69.7 (C-5'), 67.6 (C-2), 66.6 (C-3), 62.4 (C-5), 60.0 (C-6), 53.7 (C-1'), 53.0 (C-1), 28.7 (C-4'), 23.2 (C-3'), 21.9 (C-2'). $[\alpha]^{20}_D$ = +6.00 (c = 0.10, MeOH). IR/cm^{-1}: 3362, 2924, 1676, 1437, 1204, 1134, 1074. HRMS: found 434.23349 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((2'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (15):



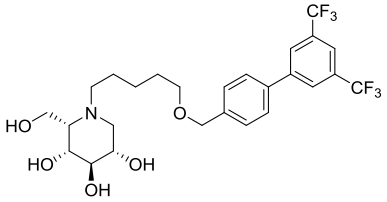
15 (9.1 mg, 0.021 mmol, 4% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.16 (m, 8H, H_{Ar} BiPh), 4.59 (s, 2H, H_2-6'), 4.04 (br s, 1H, H-4), 4.01 – 3.93 (m, 3H, H_2-6, H-2), 3.89 (t, *J* = 3.7 Hz, 1H, H-3), 3.60 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.57 – 3.45 (m, 2H, H-5, H-1a), 3.39 – 3.32 (m, 3H, H-1b, H_2-1'), 1.98 – 1.70 (m, 4H, H_2-2', H_2-4'), 1.56 – 1.52 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 162.3 – 131.8 (C_q BiPh), 130.4 – 116.9 (C_{Ar} BiPh), 73.6 (C-6'), 72.4 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.2 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = +3.64 (c = 0.22, MeOH). IR/cm^{-1}: 3377, 2866, 2324, 1670, 1204, 1136, 1074. HRMS: found 434.23350 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((4'-Trifluoromethyl[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (16):



16 (1.3 mg, 0.003 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.82 (d, *J* = 8.1 Hz, 2H, H_{Ar} BiPh), 7.74 (d, *J* = 8.2 Hz, 2H, H_{Ar} BiPh), 7.70 – 7.59 (m, 2H, H_{Ar} BiPh), 7.53 – 7.42 (m, 2H, H_{Ar} BiPh), 4.57 (s, 2H, H_2-6'), 4.10 – 3.63 (m, 5H, H-4, H_2-6, H-2, H-3), 3.57 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.49 – 3.38 (m, 2H, H-5, H-1a), 3.35 – 3.23 (m, 3H, H_2-1', H-1b), 2.02 – 1.56 (m, 2H, H_2-2'), 1.51 – 1.28 (m, 4H, H_2-4', H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 145.9 (C-7), 140.2, 130.3, 129.5 (C_q BiPh), 128.5 – 126.8 (C_{Ar} BiPh), 73.5(C-6'), 72.3(C-4), 71.2(C-5'), 69.0(C-2), 66.3(C-3), 63.9 (C-5), 55.1 (C-6), 52.9 (C-1'), 52.3 (C-1), 33.1 (C-4'), 30.3 (C-3'), 24.7 (C-2'). $[\alpha]^{20}_D$ = +20.00 (c = 0.01, MeOH). IR/cm^{-1}: 3402, 2930, 2349, 1683, 1506, 1203, 1130, 1070. HRMS: found 484.23023 $[C_{25}H_{32}F_3NO_5+H]^+$, calculated for $[C_{25}H_{32}F_3NO_5+H]^+$ 484.23053.

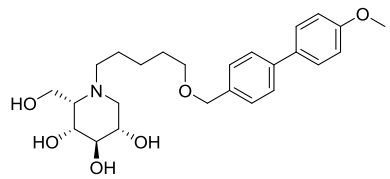
_N_-[5-((3',5'-Bis(trifluoromethyl)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (17):



17 (24.5 mg, 0.04 mmol, 8.9% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 1.6 Hz, 2H, H_{Ar} BiPh), 7.95 (s, 1H, H_{Ar} BiPh), 7.77 – 7.70 (m, 2H, H-BiPh), 7.52 (d, *J* = 8.0 Hz, 2H, H-BiPh), 4.59 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.87 (t, *J* = 4.0 Hz, 1H, H-3), 3.58 (t, *J* = 6.2 Hz,

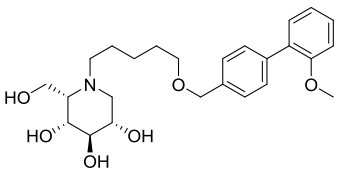
2H, H_2-5'), 3.53 – 3.47 (m, 2H, H-5, H-1a), 3.37 – 3.31 (m, 3H, H-1b, H_2-1'), 2.03 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 144.7, 141.0, 138.5, 133.5, 133.2 (C_q BiPh, CF_3), 129.7 – 121.8 (C_{Ar} BiPh), 73.4 (C-6'), 72.4 (C-4), 71.2 (C-5'), 69.0 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.2 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = +4.23 (c = 0.52, MeOH). IR/cm^{-1}: 3331, 2930, 2862, 1674, 1456, 1383, 1278, 1132, 1057. HRMS: found 552.21748 $[C_{26}H_{31}F_6NO_5+H]^+$, calculated for $[C_{26}H_{31}F_6NO_5+H]^+$ 552.21792.

N-[5-((4'-Methoxy[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (18):



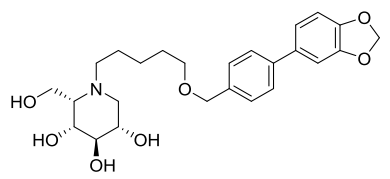
18 (4.6 mg, 0.01 mmol, 2% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.51 (m, 4H, H_{Ar} BiPh), 7.41 – 7.35 (m, 2H, H_{Ar} BiPh), 7.04 – 6.93 (m, 2H, H_{Ar} BiPh), 4.53 (s, 2H, H_2-6'), 4.01 (d, *J* = 3.0 Hz, 1H, H-4), 3.99 – 3.89 (m, 3H, H_2-6, H-2), 3.86 (d, *J* = 3.7 Hz, 1H, H-3), 3.83 (s, 3H, OMe), 3.56 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.54 – 3.43 (m, 2H, H-5, H-1a), 3.32 – 3.26 (m, 3H, H-1b, H_2-1'), 1.98 – 1.65 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 – 138.1 (C_q BiPh), 129.5, – 115.3 (C_{Ar} BiPh), 73.7 (C-6'), 72.4 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.7 (C-7'), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = -5.71 (c = 0.07, MeOH). IR/cm^{-1}: 3449, 2957, 2345, 2620, 1682, 1506, 1204, 1186, 1134. HRMS: found 446.25320 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

N-[5-((2'-Methoxy[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (19):



19 (11.6 mg, 0.026 mmol, 5% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.44 (m, 2H, H_{Ar} BiPh), 7.35 (d, *J* = 8.1 Hz, 2H, H_{Ar} BiPh), 7.34 – 6.94 (m, 4H, H_{Ar} BiPh), 4.53 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.98 – 3.93 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.8 Hz, 1H, H-3), 3.78 (s, 3H, OMe), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.44 (m, 2H, H-5, H-1a), 3.34 – 3.30 (m, 3H, H-1b, H_2-1'), 1.99 – 1.63 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 157.9, 139.6, 138.2 (C_q BiPh), 131.6 – 112.6 (C_{Ar} BiPh), 73.8 (C-6'), 72.3 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 56.0 (C-7'), 55.0 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +3.33 (c = 0.24, MeOH). IR/cm^{-1}: 3323, 2943, 2857, 2311, 1674, 1487, 1202, 1134, 1074. HRMS: found 446.25351 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

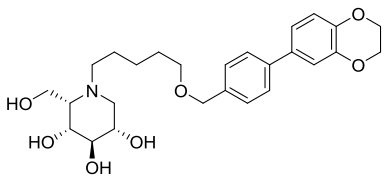
N-[5-((3',4'-*O*-Methylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (20):



20 (2.5 mg, 0.005 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.60 – 7.48 (m, 2H, H_{Ar} BiPh), 7.41 – 7.31 (m, 2H, H_{Ar} BiPh), 7.14 – 7.06 (m, 2H, H_{Ar} BiPh), 6.88 (d, *J* = 8.7 Hz, 1H, H_{Ar} BiPh), 5.98 (s, 2H, H_2-7'), 4.53 (s, 2H, H_2-6'), 4.03 – 4.01 (m, 1H, H-4), 3.98 – 3.90 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.8 Hz, 1H, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.44 (m, 2H, H-5, H-1a), 3.34 – 3.30 (m, 2H, H_2-1'), 2.02 – 1.74 (m, 1H, H-2'a), 1.74 – 1.65 (m, 3H, H-2'b, H_2-4'), 1.56 – 1.44 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 149.7, 141.7, 138.4, 136.4 (C_q BiPh), 129.4 – 102.5 (C_{Ar} BiPh), 102.5 (C-7'), 73.6 (C-6'), 72.3 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.1 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = -6.67 (c = 0.06, MeOH). IR/cm^{-1}: 3400, 2918, 1674, 1506, 1202,

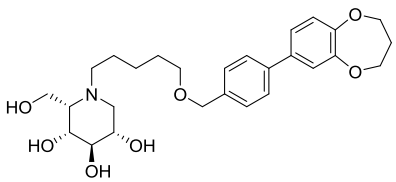
1184, 1070, 1040. HRMS: found 460.23277 $[C_{25}H_{33}NO_7+H]^+$, calculated for $[C_{25}H_{33}NO_7+H]^+$ 460.23298.

N-[5-((3',4'-*O*-Ethylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (21):



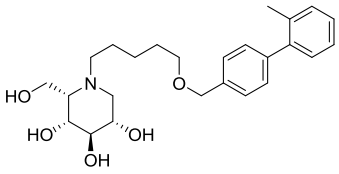
21 (26.4 mg, 0.06 mmol, 11% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.47 (m, 2H, H_{Ar} BiPh), 7.36 (d, *J* = 7.9 Hz, 2H, H_{Ar} BiPh), 7.08 (dd, *J* = 7.8, 1.6 Hz, 2H, H_{Ar} BiPh), 6.94 – 6.79 (m, 1H, H_{Ar} BiPh), 4.51 (s, 2H, H_2-6'), 4.26 (d, *J* = 1.3 Hz, 4H, H_2-7', H_2-8'), 4.02 (br s, 1H, H-4), 3.99 – 3.91 (m, 3H, H_2-6, H-2), 3.87 (t, *J* = 3.7 Hz, 1H, H-3), 3.54 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.51 – 3.41 (m, 2H, H-5, H-1a), 3.36 – 3.25 (m, 3H, H-1b, H_2-1'), 1.91 – 1.62 (m, 4H, H_2-2', H_2-4'), 1.50 – 1.46 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 145.2, 144.7, 141.3, 138.3, 135.4 (C_q BiPh), 129.4 – 116.5 (C_{Ar} BiPh), 73.7 (C-6'), 72.4 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.0 (C-3), 65.7 (C-7', C-8'), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +5.20 (c = 0.50, MeOH). IR/cm^{-1}: 3306, 2932, 2870, 1674, 1497, 1435, 1037, 1202, 1130, 1069. HRMS: found 474.24832 $[C_{26}H_{35}NO_7+H]^+$, calculated for $[C_{26}H_{35}NO_7+H]^+$ 474.24863.

N-[5-((3',4'-*O*-Propylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (22):



22 (15.9 mg, 0.032 mmol, 6% yield) was synthesized according to Suzuki-Miyamura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.57 – 7.49 (m, 2H, H_{Ar} BiPh), 7.38 (d, *J* = 8.0 Hz, 2H, H_{Ar} BiPh), 7.25 – 7.12 (m, 2H, H_{Ar} BiPh), 7.01 (d, *J* = 8.2 Hz, 1H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.19 (q, *J* = 5.3 Hz, 4H, H_2-7', H_2-9'), 4.05 – 3.84 (m, 5H, H-4, H_2-6 H-2, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.42 (m, 3H, H_2-5, H-1a), 3.36 – 3.29 (m, 3H, H-1b, H_2-1'), 2.18 (p, *J* = 5.5 Hz, 2H, H_2-8'), 1.95 – 1.80 (m, 1H, H-2'a), 1.79 – 1.62 (m, 3H, H-2'b, H_2-4'), 1.51 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 153.0 – 137.6 (C_q BiPh), 129.4 – 121.0 (C_{Ar} BiPh), 73.6 (C-6'), 72.3 (C-4), 72.0 (C-7', C-9'), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 33.3 (C-8'), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +3.13 (c = 0.32, MeOH). IR/cm^{-1}: 3381, 2872, 2324, 1684, 1522, 1310, 1204, 1134, 1065. HRMS: found 488.26396 $[C_{27}H_{37}NO_7+H]^+$, calculated for $[C_{27}H_{37}NO_7+H]^+$ 488.26428.

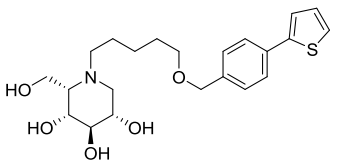
N-[5-((2'-Methyl[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (23):



23 (20.4 mg, 0.05 mmol, 10% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.43 – 7.09 (m, 8H, H_{Ar} BiPh), 4.56 (s, 2H, H_2-6'), 4.03 (br s, 1H, H-4), 3.99 – 3.87 (m, 3H, H_2-6, H-2), 3.89 – 3.85 (m, 1H, H-3), 3.58 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.45 (m, 2H, H-5, H-1a), 3.40 – 3.29 (m, 3H, H-1b, H_2-1'), 2.23 (s, 3H, Me), 2.00 – 1.65 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 142.9, 142.9, 138.4, 136.3 (C_q BiPh), 131.3 – 126.8 (C_{Ar} BiPh), 73.8 (C-6'), 72.3 (C-4), 71.1 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.3 (C-2'), 20.6 (C-7'). $[\alpha]^{20}_D$ = +6.25 (c = 0.45, MeOH). IR/cm^{-1}: 3318, 1670, 1437, 1277, 1204, 1074. HRMS: found 430.25863 $[C_{25}H_{35}NO_5+H]^+$, calculated for $[C_{25}H_{35}NO_5+H]^+$ 430.25880.

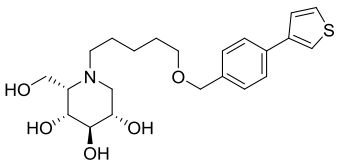
N-[5-((4-(Thiophen-2-yl)benzyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (24):

24 (2.2 mg, 0.005 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.66 – 7.58 (m, 2H, H_{Ar} BiPh), 7.40 –



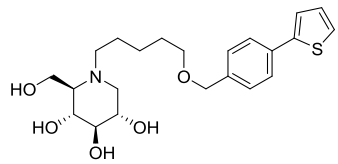
7.32 (m, 4H, H_{Ar} BiPh), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 4.00 – 3.92 (m, 3H, H_2-6, H-2), 3.86 (br s, 1H, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.44 (m, 2H, H-5, H-1a), 3.39 – 3.32 (m, 3H, H-1b, H_2-1'), 1.92 – 1.73 (m, 2H, H_2-2'), 1.73 – 1.69 (m, 2H, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 145.1, 139.1, 135.3 (C_q BiPh), 129.5 – 124.3 (C_{Ar} BiPh), 73.6 (C-6'), 72.4 (C-4), 71.0 (C-5'), 69.0 (C-2), 68.1 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.5 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = -3.57 (c = 0.056, MeOH). IR/cm^{-1}: 3366, 2924, 2326, 2872, 2326, 2207, 1684, 1506, 1202, 1134, 1101. HRMS: found 422.19949 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-3-yl)benzyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (25):



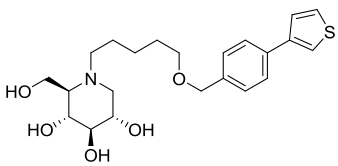
25 (10.0 mg, 0.024 mmol, 5% yield) was synthesized according to Suzuki coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.69 – 7.59 (m, 3H, H_{Ar} BiPh), 7.48 – 7.44 (m, 2H, H_{Ar} BiPh), 7.37 (d, *J* = 8.0 Hz, 2H, H_{Ar} BiPh), 4.51 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.99 – 3.91 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.7 Hz, 1H, H-3), 3.55 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.53 – 3.41 (m, 2H, H-5, H-1a), 3.31 – 3.15 (m, 3H, H-1b, H_2-1'), 1.96 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.51 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 141.8, 137.1, 135.3 (C_q BiPh), 128.1 – 119.9 (C_{Ar} BiPh), 72.3 (C-6'), 70.9 (C-4), 69.5 (C-5'), 67.5 (C-2), 66.6 (C-3), 62.4 (C-5), 60.0 (C-6), 53.6 (C-1'), 53.0 (C-1), 28.7 (C-4'), 23.2 (C-3'), 21.8 (C-2'). $[\alpha]^{20}_D$ = +9.00 (c = 0.20, MeOH). IR/cm^{-1}: 3319, 2926, 2862, 1674, 1427, 1201, 1134, 1072. HRMS: found 422.19946 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-2-yl)benzyl]-4-yl)-methoxy)-pentyl]-1-deoxynojirimycin (26):



26 (1.8 mg, 0.004 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (600 MHz, MeOD) δ 7.55 – 7.44 (m, 2H, H_{Ar} BiPh), 7.39 – 7.17 (m, 5H, H_{Ar} BiPh), 4.47 (s, 2H, H_2-6'), 4.10 (d, *J* = 12.4 Hz, 1H, H-6a), 3.88 (dd, *J* = 12.5, 3.1 Hz, 1H, H-6b), 3.67 (ddd, *J* = 11.5, 9.2, 5.0 Hz, 1H. H-2), 3.59 (t, *J* = 9.8 Hz, 1H, H-4), 3.53 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.44 (dd, *J* = 12.0, 4.9 Hz, 1H, H-1a), 3.39 – 3.35 (m, 1H, H-1'a), 3.36 (t, *J* = 9.2 Hz, 1H, H-3), 3.22 – 3.14 (m, 1H, H-1'b), 3.02 (dd, *J* = 10.3, 2.9 Hz, 1H, H-5), 2.97 (t, *J* = 11.7 Hz, 1H, H-1b), 1.89 – 1.73 (m, 2H, H_2-2'), 1.72 – 1.66 (m, 2H, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 140.1, 139.2 (C_q BiPh), 132.5 – 122.3 (C_{Ar} BiPh), 78.2 (C-3), 73.1 (C-6'), 71.1 (C-5'), 68.8 (C-4), 67.8 (C-2), 67.4 (C-5), 54.9 (C-6), 54.8 (C-1), 54.3 (C-1'), 30.1 (C-4'), 24.5 (C-3'), 23.9 (C-2'). $[\alpha]^{20}_D$ = -4.00 (c = 0.20, MeOH). IR/cm^{-1}: 3402, 2943, 2868, 2324, 2241, 1683, 1205, 1134. HRMS: found 422.19961 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-3-yl)benzyl]-4-yl)-methoxy)-pentyl]-1-deoxynojirimycin (27):



27 (2.5 mg, 0.006 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.67 – 7.59 (m, 3H, H_{Ar} BiPh), 7.50 – 7.43 (m, 2H, H_{Ar} BiPh), 7.40 – 7.35 (m, 2H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.10 (d, *J* = 12.4 Hz, 1H, H-6a), 3.88 (dd, *J* = 12.5, 3.2 Hz, 1H, H-6b), 3.66 (ddd, *J* = 11.3, 9.3, 4.9 Hz, 1H, H-2), 3.59 – 3.57 (m, 1H, H-4), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.43 (dd, *J* = 12.1, 5.0 Hz, 1H, H-1a), 3.37 (dt, *J* = 12.8, 4.9 Hz, 1H, H-1'a), 3.35 (t, *J* = 9.3 Hz, 1H, H-3), 3.19 (td, *J* = 12.5, 5.0 Hz, 1H, H-1'b), 3.01 (dd, *J* = 10.4, 3.0 Hz, 1H, H-5), 2.97 (t, *J* = 11.7 Hz, 1H, H-1b), 1.86 – 1.73 (m, 2H, H_2-2'), 1.72 – 1.68 (m, 2H. H_2-4'), 1.55 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 143.2, 138.5 (C_q BiPh), 136.7

– 121.3 (C_{Ar} BiPh), 78.2 (C-3), 73.7 (C-6'), 70.9 (C-5'), 68.8 (C-4), 67.8 (C-2), 67.4 (C-5), 54.9 (C-6), 54.8 (C-1), 54.3 (C-1'), 30.1 (C-4'), 24.5 (C-3'), 23.9 (C-2'). $[\alpha]^{20}_{D}$ = -15.00 (c = 0.20, MeOH). IR/cm^{-1}: .3364, 2918, 2349, 1670, 1506, 1205, 1138. HRMS: found 422.19948 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

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6 Synthesis and Biological Evaluation of *N*-substituted α-Geminal Bis-hydroxymethyl Piperidine Iminosugars

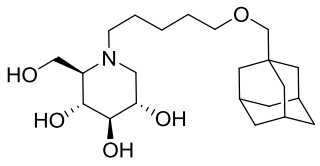
Introduction

Deoxynojirimycin (DNJ) and its congeners are inhibitors of a wide variety of glycosidases as well as some glycosyltransferases. *N*-alkyl DNJ derivatives have been identified as compounds with considerable therapeutic potential for the treatment of various diseases including diabetes and several lysosomal storage disorders (LSDs). Two characteristic iminosugars often included in studies aimed for the design of glycoprocessing enzymes are the natural product, DNJ, and its C-5 epimer, L-*ido*-DNJ.[1] *N*-butyl-DNJ is a moderately potent

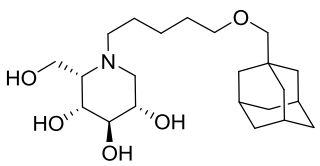
glucosylceramide synthase (GCS) inhibitor and based on this virtue used in the clinic for the treatment of Gaucher disease in what is termed substrate reduction therapy. Enlarging the substituent on the DNJ nitrogen improves GCS inhibitory potency, but at the same time results in more potent off-target inhibition. Similarly substituted, L-*ido*-configured iminosugars appear to be much cleaner: they inhibit GCS with equal or (slightly) superior potency compared to their DNJ counterparts and are, with the exception of neutral glucosylceramidase (GBA2), remarkably more selective. These observations invite the question, which underlies the work described in this Chapter, whether hybrid piperidines bearing two α-geminal hydroxymethyl moieties (thus featuring both DNJ and L-*ido*-DNJ hydroxymethyls) would be valid GCS inhibitors, and if so, would be (even) more selective than existing *N*-alkyl-iminosugars.

Figure 1 depicts the lead-iminosugars that led to the studies described here. *N*-AMP-DNJ (**1**, MZ-21) is a potent GCS/GBA1/GBA2 inhibitor, and its L-*ido* congener (**2**, MZ-31), has (slightly) improved GCS/GBA2 inhibitory potency offset by considerable loss in GBA1 inhibitory activity. *N*-AMP D-*galacto* DNJ (**3**) and *N*-AMP L-*altro* DNJ (**4**) are the C-4 epimers of *N*-AMP DNJ and *N*-AMP L-*ido*-DNJ, respectively. Compound **3** is a moderately potent GCS inhibitor and a potent GBA2 inhibitor, and intestinal glycosidases are also inhibited by this compound. Epimer **4** in contrast is only a moderate GBA2 inhibitor with low or no inhibition of intestinal glycosidases, GCS and GBA1.

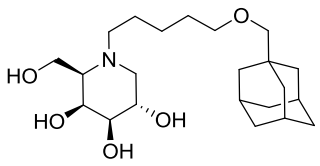
***Figure 1**: IC50 values of N-AMP DNJ isosteres for GlcCer metabolizing enzymes*



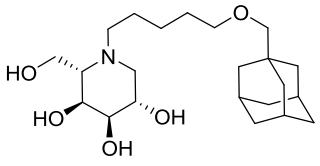
1, MZ-21 IC_{50} GCS 200 nM
IC_{50} GBA1 0.1 μM
IC_{50} GBA2 2 nM



2, MZ-31 IC_{50} GCS 100 nM
IC_{50} GBA1 30 μM
IC_{50} GBA2 1 nM



3 *IC_{50} GCS 500 nM
*IC_{50} GBA1 0.2 μM
*IC_{50} GBA2 <1 nM

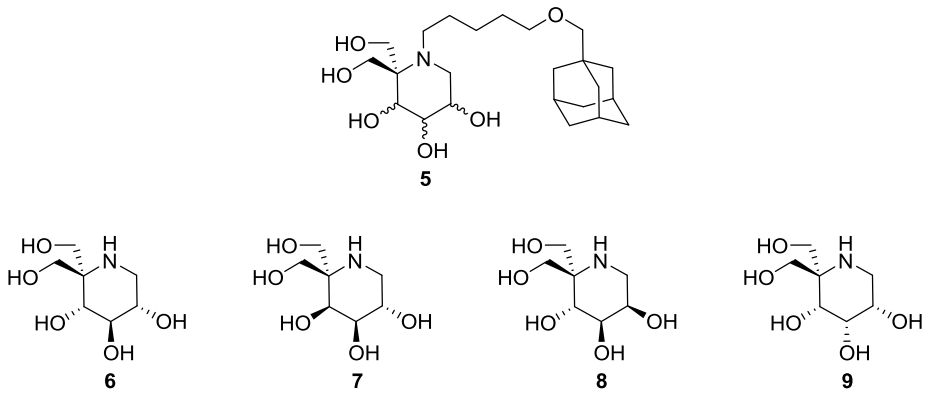


4 *IC_{50} GCS >100 μM
*IC_{50} GBA1 30 μM
*IC_{50} GBA2 500 nM

*IC_{50} data from Wennekes *el al.*[1]

These findings led to the design of a number of hybrid iminosugars bearing two geminal hydroxymethyl substituents, as depicted in Figure 2. The list of target compounds encompasses the configurational D-*gluco*-L-*ido* (**6**) and D-*galacto*-L-*altro* (**7**) pairs, but also a choice number of compounds emulating in configuration other pyranosides and that may be of interest in their own right (**8**, **9** and their *N*-alkyl derivatives).

Figure 2: *Structures of N-AMP α-geminal bishydroxymethyl iminosugars*

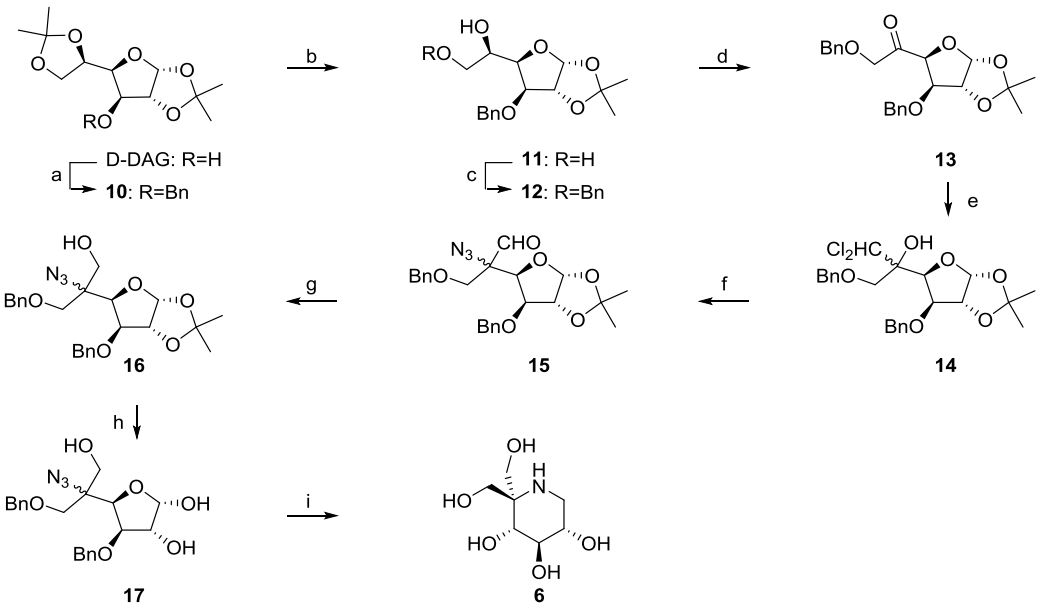


Results and discussion

Synthesis of 5-*C*-hydroxymethyl-DNJ (6)

Pawar *et al.* documented the synthesis of α-geminal bishydroxymethyl piperidines, which was adopted in the synthesis of D-*gluco*-L-*ido* configured compounds **6** and its C-2 and C-3 epimers.[2] In the first instance, the synthesis of D-*gluco*-L-*ido* DNJ (**6**) was undetaken following the literature procedure (Scheme 1).[2] Correspondingly, D-diacetone glucose (D-DAG) was treated with sodium hydride and benzyl bromide to give **10**. Protonolysis of **10** afforded diol **11**. Regioselective benzylation under the agency of dibutyltin oxide, sodium hydride and benzyl bromide afforded **12** in high yield. The secondary alcohol in **12** was oxidized using PCC to yield ketone **13**. *In situ* formation of dichloromethane carbanion, from dichloromethane and lithium di-isopropyl amide, and subsequent addition to ketone **13** afforded methylene dichloride **14**. An α-azido group was introduced at C-5 in **14** via a Jocic Reeve reaction to give **15**. Azido-aldehyde **15** was reduced using sodium borohydride to afford azido alcohol **16**. Demasking of the isopropylidene protecting group, followed by hydrogenation and subsequent reductive amination yielded the target α-geminal bishydroxymethyl DNJ **6** in an overall yield of 6%.

***Scheme 1**: Synthesis of 5-C-hydroxymethyl-1-deoxynojirimycin (**6**)*



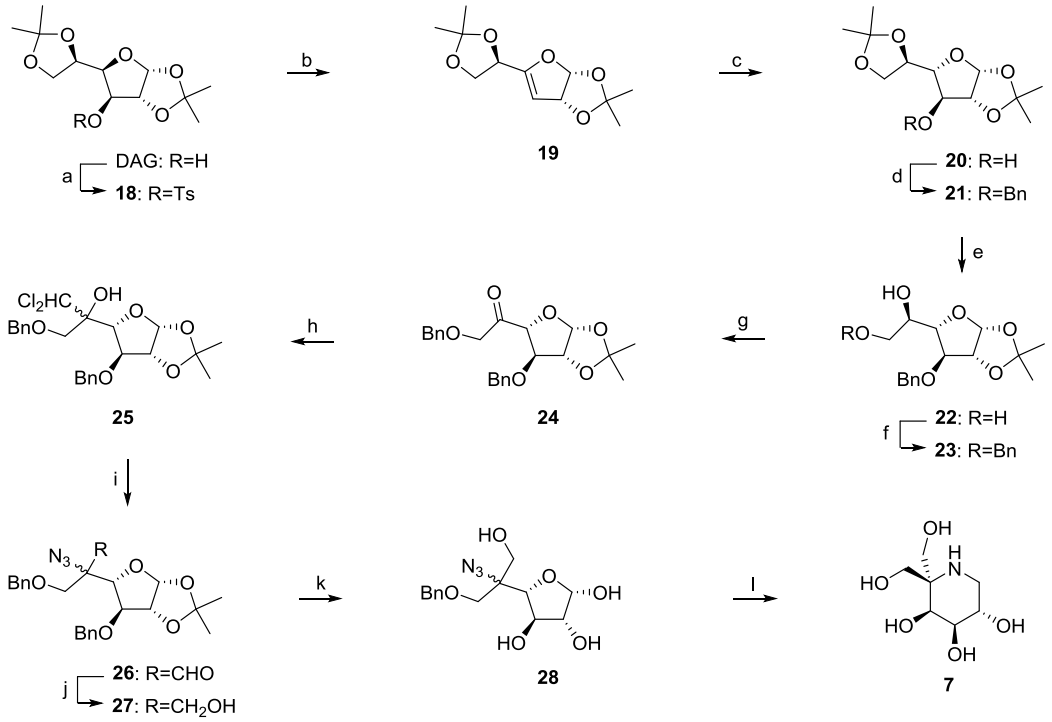
Reagents and conditions: [**a**] NaH, BnBr, DMF, 97%; [**b**] AcOH, H_2O, 80%; [**c**] 1) Bu_2SnO, toluene, 2) NaH, BnBr, 90%; [**d**] PCC, DCM, 53%; [**e**] LDA, DCM, THF, 55%; [**f**] NaN_3, DMF, TBAI, 115 °C, 69%; [**g**] $NaBH_4$, 89%; [**h**] TFA, H_2O, 68%; [**i**] H_2, Pd/C, 5 bar, 74%.

Synthesis of 5-*C*-hydroxymethyl-1-deoxy-D-galactonojirimycin (7)

It was anticipated that the chemical transformation depicted in Scheme 1 could also be applied on the C-4 epimer of diacetone glucose: diacetone galactose, which would give access to D-*galacto*-L-*altro*-iminosugar **7**. Tosylation of DAG[3] and subsequent β-elimination of tosylate **18** gave glycal **19**[4] in high yield (Scheme 2). Hydroboration and subsequent diastereoselective oxidation afforded the desired diacetone galactose **20** in good yield.[5] Compound **20** was subjected to the transformations as outlined above for the synthesis of **6**. The hydroxyl functionality in **20** was protected using benzyl bromide to give **21**. Isopropylidene demasking of **21** with aqueous acidic acid afforded diol **22**. Regioselective benzylation with the aid of dibutyltin oxide afforded **23**. Alcohol **23** was oxidized with PCC to give ketone **24**. The key step in this synthesis is the introduction of dichloromethylene onto the 5-ketone **24** to form **25**, a reaction that proceeded in an even better yield than that on glucose isomer **14**. Compound **25** was next reacted with sodium azide in DMF at 115 °C to uneventfully give **26** in a yield of 93%. Aldehyde **26** was reduced to give alcohol **27**, which underwent a TFA-water hydrolysis to remove the isopropyl protecting group after which the resulting intermediate **28** was exposed

to 5 bar H_2 atmosphere and a catalytic amount of palladium on carbon to remove the benzyls, reduce the azide to the amine and effect an ensuing intramolecular reductive amination to yield target iminosugar **7** (12% over 12 steps).

***Scheme 2**: Synthesis of 5-C-hydroxymethyl-1-deoxy-D-galactonojirimycin (**7**)*

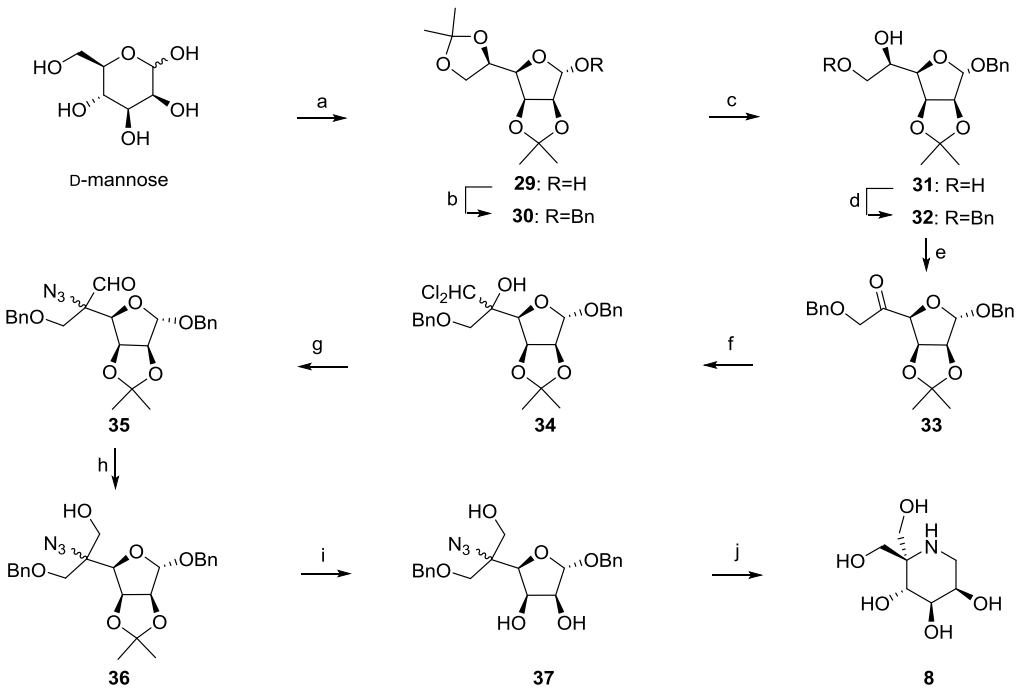


Reagents and conditions: [**a**] *p*-TsCl, pyridine, DCM, 60 °C, 98%; [**b**] *t*BuOK, THF, 0 °C, 91%; [**c**] 1) BH_3·THF, THF; 2) NaOH, H_2O_2, 75%; [**d**] NaH, BnBr, DMF; [**e**] AcOH, H_2O, 86%, 2 steps; [**f**] 1) Bu_2SnO, tol, 2)TBABr, BnBr, 82%; [**g**] PCC, DCM, 92%; [**h**] LDA, DCM, -78 °C, 74%; [**i**] NaN_3, TBAI, DMF, 115 °C, 93%; [**j**] $NaBH_4$, MeOH, 0 °C, 82%; [**k**] TFA, H_2O, 0 °C, 63%; [**l**] Pd/C, H_2, EtOH, 5 bar, 91%.

Synthesis of 5-*C*-hydroxymethyl-1-deoxy-D-mannonojirimycin (8) and 5-*C*-hydroxymethyl-1-deoxy-D-allonojirimycin (9)

The D-*manno*-L-*gulo* iminosugar **8** and D-*allo*-L-*talo* iminosugar **9** were synthesized as described by Pawar *et al.*[2] The synthesis of **8** starts with TBATB catalyzed isopropylidenation of D-mannose to give **29**.[6] Benzylation of **29** gained **30** and subsequent acidic hydrolysis of the acetal protecting group afforded **31**. Alcohol **31** underwent the 7-step transformation as described above for the preparation of **6** and **7**, which generated **8** in an overall yield of 9% (10 steps).

***Scheme 3**: Synthesis of 5-C-hydroxymethyl-1-deoxy-D-mannonojirimycin (**8**)*

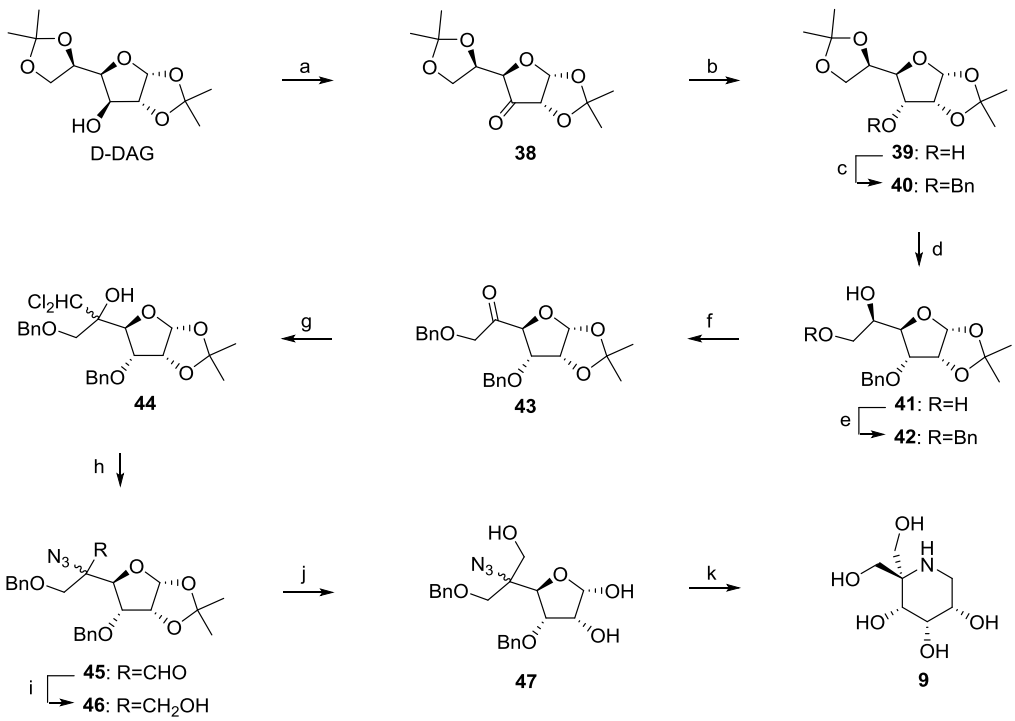


Reagents and conditions: [**a**] TBATB, acetone, 64%; [**b**] 18-crown-6, BnBr, KOH, THF, 75%; [**c**] AcOH, H_2O, r.t., 81%; [**d**] 1) Bu_2SnO, tol; 2) BnBr, TBABr, 76%; [**e**] PCC, DCM, 30 °C, 88%; [**f**] LDA, THF, -78 °C, 66%; [**g**] NaN_3, TBAI, DMF, 115 °C, 87%; [**h**] $NaBH_4$, MeOH, 0 °C, 80%; [**i**] TFA, H_2O, 0 °C, 45%; [**j**] Pd/C, H_2, EtOH, 5 bar, 82%.

In a similar vein, diacetone allose **39**, obtained via oxidation and stereoselective reduction from D-DAG, was transformed to produce compound **9** (Scheme 4). The C-3 alcohol of D-DAG was oxidized to form aldehyde **38**, which was reduced by sodium borohydride to give diacetone D-allose **39** in 74% yield over the 2 steps. Compound **9** was prepared from **39** as described previously for the synthesis of **6** with an overall yield of 9% in 9 steps.

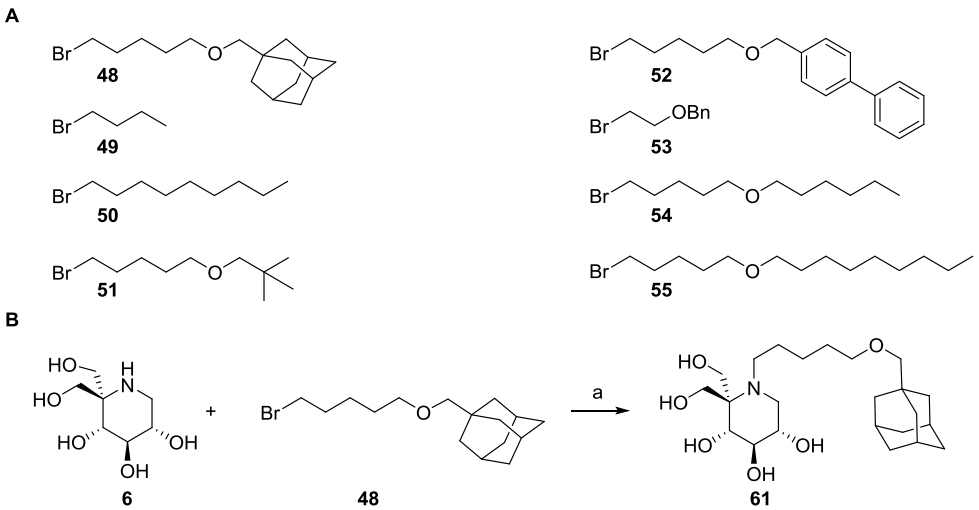
With the four α-geminal bis-(hydroxymethyl) piperidines (**6**, **7**, **8** and **9**) in hand, the target hydrophobic iminosugars were prepared by treating **6** - **9** with bromides **48** – **55** (Scheme 5A; see for the final structures Figures 4, 5, 6 and 7). As an example, the synthesis of *N*-AMP D-*gluco*-L-*ido* DNJ (**61**) is depicted in Scheme 5B. Treatment of D-*gluco*-L-*ido* DNJ (**6**) with bromide **48** and potassium carbonate in DMF gave **61** in 11% yield (Scheme 5B). Yields of the *N*-alkyl derivatives vary from 2% to 46% after HPLC purification (see the experimental section for details).

***Scheme 4**: 5-C-Hydroxymethyl-1-deoxy-D-allonojirimycin (**9**)*



Reagents and conditions: [**a**] PCC, DCM, 81%; [**b**] $NaBH_4$, EtOAc, H_2O, 92%; [**c**] NaH, BnBr, DMF, 90%; [**d**] AcOH, H_2O, 46%; [**e**] 1) Bu_2SnO, tol; 2) BnBr, TBABr, 76%; [**f**] PCC, DCM, 64%; [**g**] DCM, LDA, THF, -78 °C, 99%; [**h**] NaN_3, DMF, 115 °C, 71%; [**i**] $NaBH_4$, MeOH, 0 °C, 81%; [**j**] TFA, H_2O, 0 °C, 70%; [**k**] Pd/C, H_2, EtOH, 5 bar, 81%.

***Scheme 5**: N-alkylation of α-geminal hydroxymethyl iminosugars*

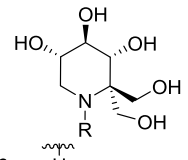


Reagents and conditions: [**a**] K_2CO_3, DMF, 80 °C, 11%.

Biological evaluation

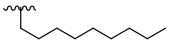
D-*Gluco*-L-*ido* hybrid iminosugars

Figure 3: *Enzyme inhibition assay results: IC_{50} values, for D-gluco-L-ido DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparision with the corresponding D-gluco-DNJ and L-ido-DNJ analogues*

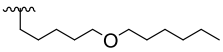


6 H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 32 μM

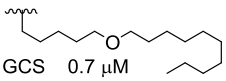
56
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 515 μM



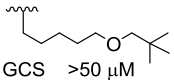
57
IC_{50} GCS 45 μM
IC_{50} GBA1 81 μM
IC_{50} GBA2 0.15 μM



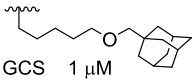
58
IC_{50} GCS 3.5 μM
IC_{50} GBA1 54 μM
IC_{50} GBA2 0.15 μM



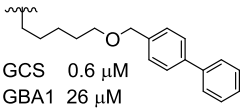
59
IC_{50} GCS 0.7 μM
IC_{50} GBA1 95 μM
IC_{50} GBA2 0.1 μM



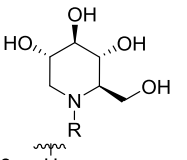
60
IC_{50} GCS >50 μM
IC_{50} GBA1 271 μM
IC_{50} GBA2 2 μM



61
IC_{50} GCS 1 μM
IC_{50} GBA1 8 μM
IC_{50} GBA2 0.03 μM

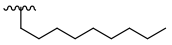


62
IC_{50} GCS 0.6 μM
IC_{50} GBA1 26 μM
IC_{50} GBA2 6 nM

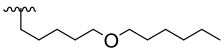


63 H
IC_{50} GCS >50 μM
IC_{50} GBA1 754 μM
IC_{50} GBA2 20 μM

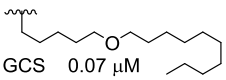
64
IC_{50} GCS 50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.3 μM



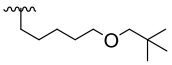
65
IC_{50} GCS 1.4 μM
IC_{50} GBA1 3 μM
IC_{50} GBA2 2 nM



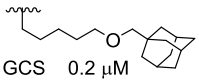
66
IC_{50} GCS 0.08μM
IC_{50} GBA1 5 μM
IC_{50} GBA2 2 nM



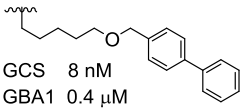
67
IC_{50} GCS 0.07 μM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 1.5 nM



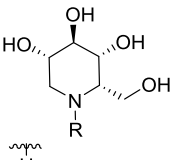
68
IC_{50} GCS 5 μM
IC_{50} GBA1 6 μM
IC_{50} GBA2 5 nM



1
IC_{50} GCS 0.2 μM
IC_{50} GBA1 0.5 μM
IC_{50} GBA2 0.8 nM

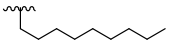


69
IC_{50} GCS 8 nM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 0.7 nM

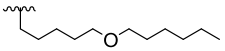


70 H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 138 μM

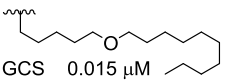
71
IC_{50} GCS 4 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.2 μM



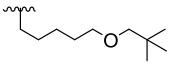
72
IC_{50} GCS 0.1 μM
IC_{50} GBA1 40 μM
IC_{50} GBA2 1 nM



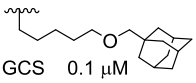
73
IC_{50} GCS 0.03 μM
IC_{50} GBA1 102 μM
IC_{50} GBA2 3 nM



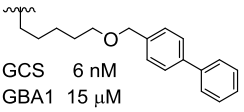
74
IC_{50} GCS 0.015 μM
IC_{50} GBA1 9 μM
IC_{50} GBA2 0.15 nM



75
IC_{50} GCS 1.6 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 nM



2
IC_{50} GCS 0.1 μM
IC_{50} GBA1 34 μM
IC_{50} GBA2 1 nM



76
IC_{50} GCS 6 nM
IC_{50} GBA1 15 μM
IC_{50} GBA2 1 nM

The D-*gluco*-L-*ido* iminosugars (**6**, **56** - **62**) were tested on their inhibitory potency against the glucosylceramide metabolizing enzymes, GCS, GBA1 and GBA2. The corresponding D-*gluco* (**1**, **63** - **69**) and L-*ido* (**2**, **70** - **76**) iminosugar derivatives were included as reference compounds to determine the effect of the additional hydroxymethyl group on the C-5 position. The results are tabulated in Figure 3. From the results it can be seen that the DNJ and L-*ido*-DNJ derivatives are without exception the more potent GCS inhibitors when compared with their D-*gluco*-L-*ido* configured α-geminal bishydroxymethyl piperidine counterparts, irrespective of the nature of the *N*-alkyl substituent. In line with what was reported previously the L-*ido* iminosugars proved to be the more potent GCS inhibitor when compared with the D-*gluco*-configured equivalent. Based on this result, it can be concluded that installment of an extra C-5 hydroxymethyl group at the carbon already bearing such a substituent is detrimental for GCS inhibition.

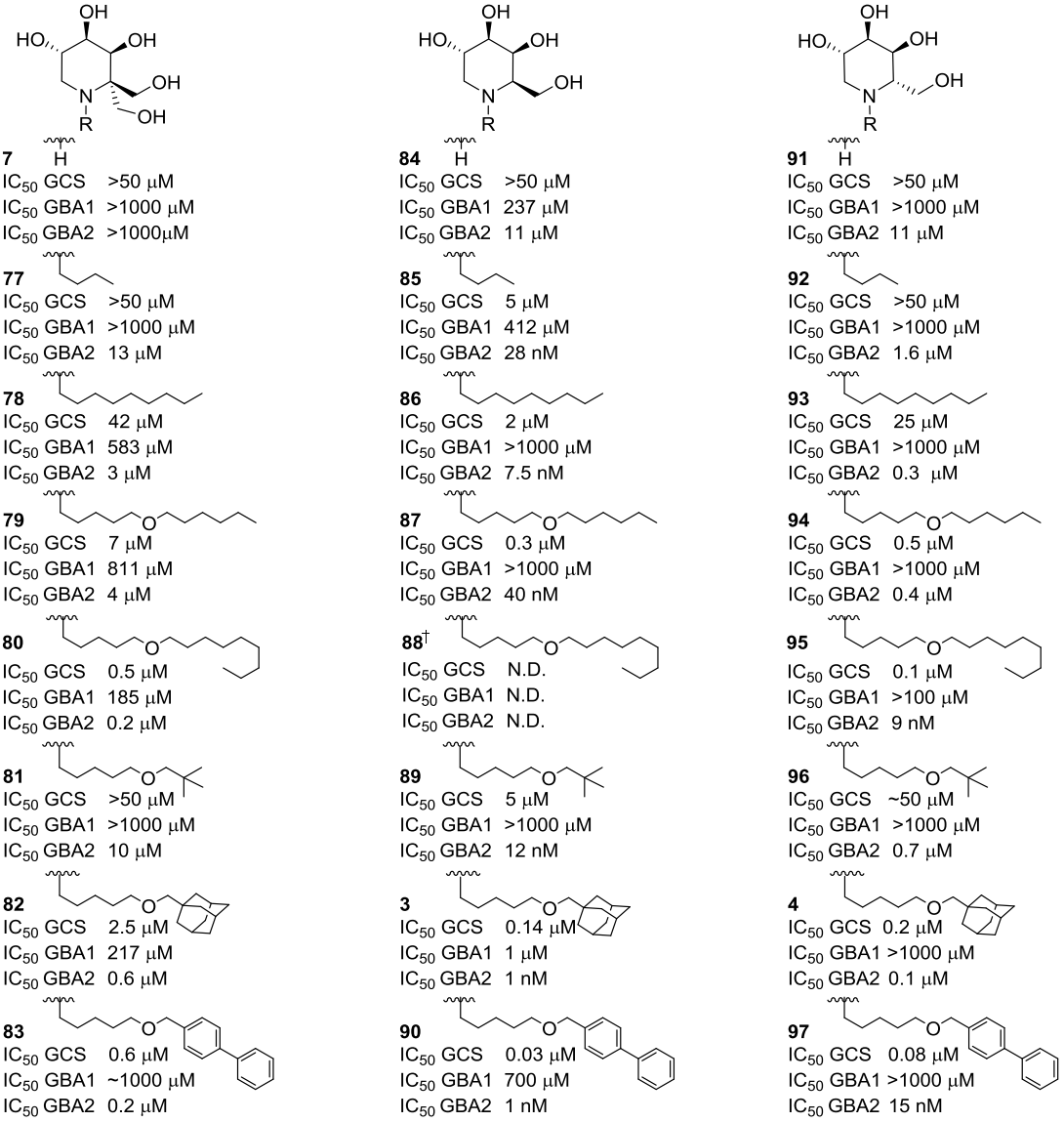
When looking at GBA1 inhibition values, it is remarkable that, whereas the hybrid iminosugars are all weaker inhibitors compared to the D-*gluco* configured molecules, they sometimes outperform their L-*ido* counterparts. This may indicate that the D-*gluco* configuration is preferred by GBA1, that an additional hydroxymethyl group may increase the steric hindrance and thus affect the inhibitory activity, but that this may be less detrimental than altering the configuration at C-5.

The effect of adding an extra hydroxymethyl at C-5 on GBA2 inhibition is as was noted for GCS inhibitory activity: the D-*gluco*-L-*ido* hybrid iminosugars are still relatively potent GBA2 inhibitors, but much less so than the corresponding D-*gluco* and L-*ido* compounds.

D-*Galacto*-L-*altro* hybrid iminosugars

In Figure 4, the inhibitory potencies towards GCS, GBA and GBA2 of the D-*galacto*-L-*altro* hybrid iminosugars (**7**, **77** - **83**) as well as that of their and the parent compounds (D-*galacto* isomers, **3**, **84** – **90**; L-*altro* isomers, **4**, **91** – **97**) are depicted. The D-*galacto*-L-*altro* hybrids do inhibit GCS to some extend, however not at the concentrations at which the D-*galacto* and L-*altro* iminosugars inhibit GCS. None of the compounds, with the exception of D-*galacto* AMP (**3**, IC_{50} GBA1 = 1 μM) inhibit GBA. In contrast, several of the D-*galacto* configured iminosugars inhibit GBA2 in the nanomolar range and are even more potent than the corresponding DNJ (i.e. **64**, **1** and **69**) and L-*ido*-DNJ derivatives (i.e. **71**, **2** and **76**). The D-*galacto*-L-*altro* hybrid compounds, though, are only weak GBA2 inhibitors, if at all, and also here it appears that the extra appendage at C-5 is detrimental for inhibition potency.

Figure 4: *Enzyme inhibition assay results: IC_{50} values, for D-galacto-L-altro-DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparision with the corresponding D-galacto-DNJ and L-altro-DNJ analogues*



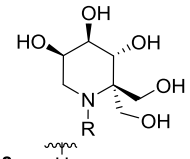
† : Compound not synthesized; N.D.: Activity not determined

D-*Manno*-L-*gulo* iminosugars

As shown in Figure 5, none of the D-*manno*-L-*gulo* hybrid iminosugars potently inhibit GCS. The most active GCS inhibitor in this series is the biphenyl derivative **104**. Remarkably, however, the hybrid molecules do sometimes outperform their D-*manno* and L-*gulo* configured

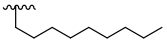
counterparts, in terms of GCS inhibitory potency (compare, for instance the GCS inhibitory potency of **102** with **110** and **118**, and **103** with **111** and **109**). The potency of this series as GBA1 and GBA2 inhibitors is modest at most.

Figure 5: *Enzyme inhibition assay results: IC_{50} values, for D-manno-L-gulo-DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparision with the corresponding D-manno-DNJ and L-gulo-DNJ analogues*

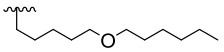


8 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

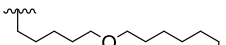
98
IC_{50} GCS 40 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 18 μM



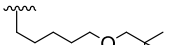
99
IC_{50} GCS >50 μM
IC_{50} GBA1 594 μM
IC_{50} GBA2 4 μM



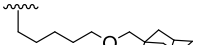
100
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 3 μM



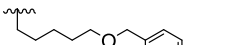
101
IC_{50} GCS >50 μM
IC_{50} GBA1 >200 μM
IC_{50} GBA2 25 μM



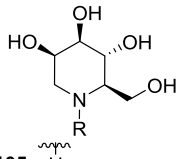
102
IC_{50} GCS 11 μM
IC_{50} GBA1 394 μM
IC_{50} GBA2 10 μM



103
IC_{50} GCS 13 μM
IC_{50} GBA1 389 μM
IC_{50} GBA2 3 μM

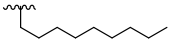


104
IC_{50} GCS 3 μM
IC_{50} GBA1 898 μM
IC_{50} GBA2 1 μM

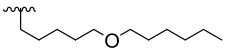


105 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >100 μM

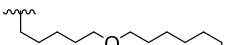
106
IC_{50} GCS ~10 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



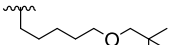
107
IC_{50} GCS >50 μM
IC_{50} GBA1 >100 μM
IC_{50} GBA2 >1000 μM



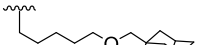
108
IC_{50} GCS 8 μM
IC_{50} GBA1 929 μM
IC_{50} GBA2 3 μM



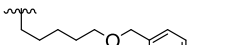
109
IC_{50} GCS >50 μM
IC_{50} GBA1 110 μM
IC_{50} GBA2 31 μM



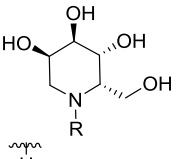
110
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



111
IC_{50} GCS >50 μM
IC_{50} GBA1 62 μM
IC_{50} GBA2 61 μM

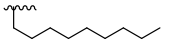


112
IC_{50} GCS 3 μM
IC_{50} GBA1 133 μM
IC_{50} GBA2 N.D.

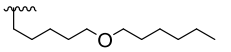


113 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

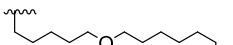
114
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



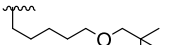
115
IC_{50} GCS >50μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 7.5 μM



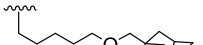
116
IC_{50} GCS 21 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 μM



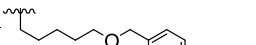
117
IC_{50} GCS 4 μM
IC_{50} GBA1 972 μM
IC_{50} GBA2 2 μM



118
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 42 μM



119
IC_{50} GCS >50 μM
IC_{50} GBA1 988 μM
IC_{50} GBA2 3 μM

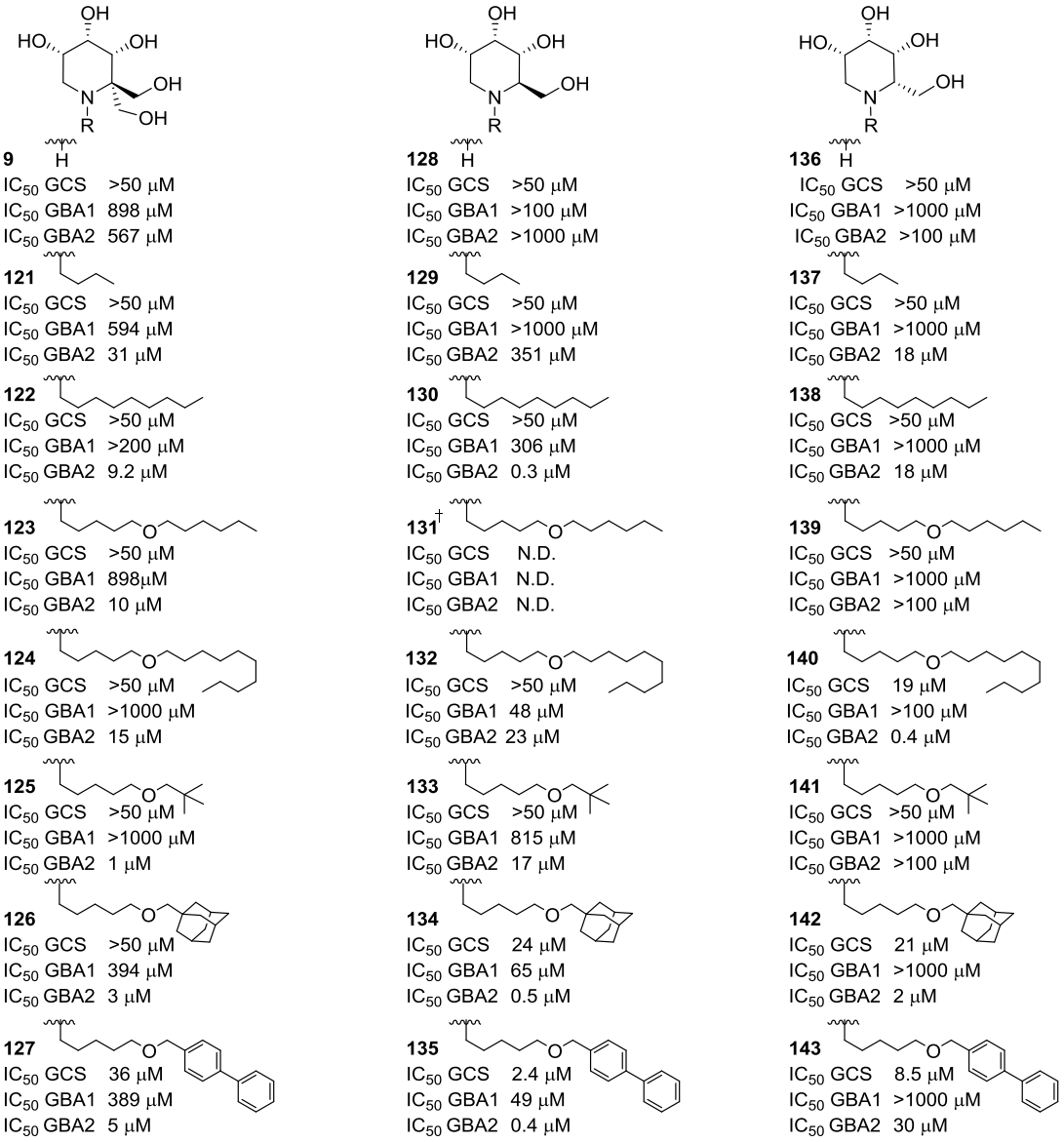


120†
IC_{50} GCS N.D.
IC_{50} GBA1 N.D.
IC_{50} GBA2 N.D.

† : Compound not synthesized; N.D.: Activity not determined

D-*Allo*-L-*talo* hybrid iminosugars

Figure 6: *Enzyme inhibition assay results: IC50 values, for D-allo-L-talo-DNJ and its N-alkyl derivatives as inhibitors of GCS, GBA1 and GBA2, in comparision with the corresponding D-allo-DNJ and L-talo-DNJ analogues*



† : Compound not synthesized; N.D.: Activity not determined

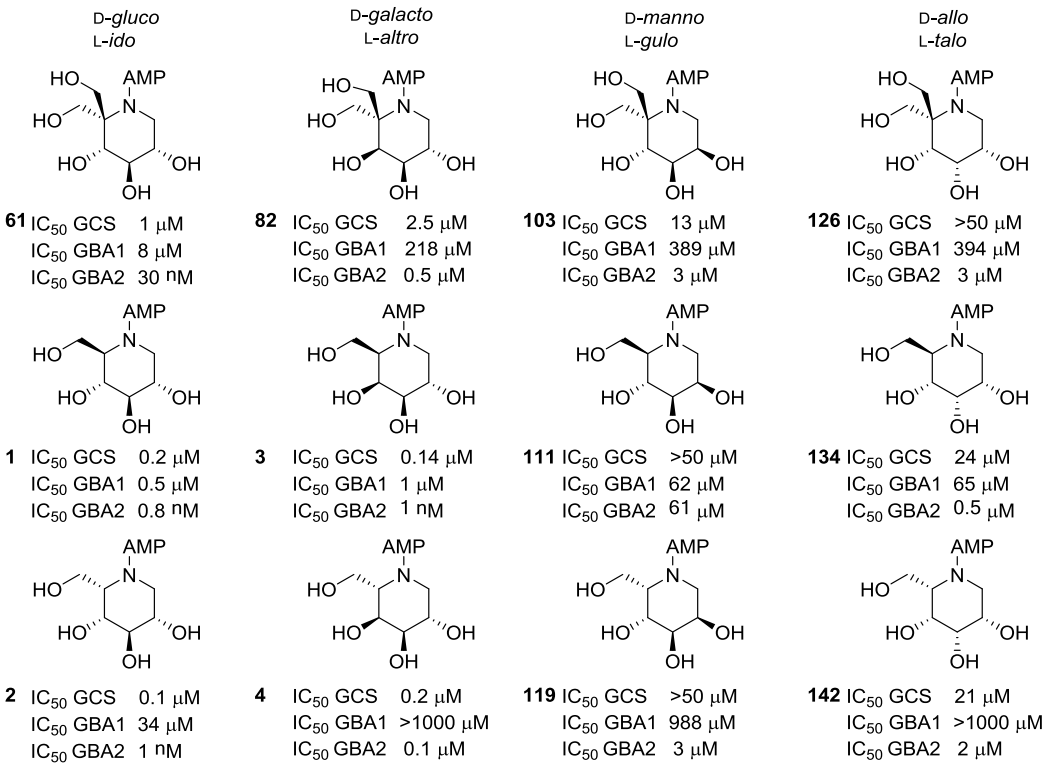
The results of the biological assays of the D-*allo*-L-*talo* hybrid iminosugar series (**9**, **121** - **127**), D-*allo* series (**128** - **135**) and L-*talo* series (**136** - **143**) are given in Figure 6. As can be

seen, the series contains no GCS/GBA/GBA2 inhibitors with remarkable potency. Obviously, the rather drastic deviation of the glucose configuration is detrimental for inhibition of the three glucose-processing enzymes, and addition of an extra hydroxymethyl does not help.

Conclusion

In this Chapter, iminosugars that encompass both the D-glucose and L-idose structural properties in one molecule as well as its C-2, C-3 and C-4 epimers were synthesized. These four sets of hybrid compounds (**6**, **7**, **8** and **9**) were *N*-alkylated with various hydrophobic substitutes which produced a library of 28 *N*-alkylated derivatives. This set and their corresponding DNJ congeners have been tested as inhibitors for the GlcCer metabolic enzymes (GCS, GBA1 and GBA2).

Figure 7: *Enzyme inhibition assay results: IC_{50} values of the N-AMP iminosugar derivatives*



Generally, the hybrid compounds are weaker GCS inhibitors compared to both D-configured and L-configured iminosugars (Figure 7), with the D-*manno*-L-*gulo* compound **103** being an exception. Concerning GBA1 inhibitory activity, the bis-hydroxymethyl compounds are

generally more potent than their corresponding L-compounds while less potent than the D-compounds. This may indicate that the D-configuration at C-5 is more beneficial for the iminosugar to bind to GBA1, and that an additional hydroxymethyl has a negative effect in binding to the active site of the enzyme. There is no specific rule observed for how the extra hydroxymethyl group affects GBA or GBA2 activity, and general trends appear the same as for GCS activity. It should be noted that many of the compounds described here are of a configuration that is rather far removed from that of glucopyranose. It may therefore well be that the compound collections may contain inhibitors for glycoprocessing enzymes other than those assayed here. It would therefore be of interest to screen the compound collections against other glycosidases, including galactosidases and mannosidases that are of interest in their own right in biological and biomedical research.

Experimental Section

Enzyme inhibition assays: The potencies (IC_{50} values) of the *N*-alkyl-DNJ derivatives as GCS, GBA1 and GBA2 inhibitors were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[7] Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbeliferyl-β-D-glucoside as substrate.[8] Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and sodium taurocholate (0.2%, w/v). Assays performed in triplicate were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm.

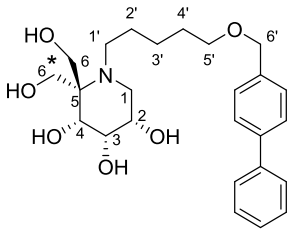
GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with 4-methylumbeliferyl-β-D-glucoside as substrate.[8] GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbeliferyl-β-D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined

with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General compound synthesis, purification and analysis methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz) or Bruker 600 (600/150 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[9] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ = 589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer, column size d = 26 mm, l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 μm, 19 x 150 mm column).

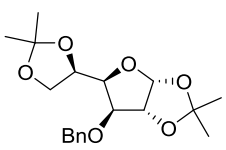
General Procedure: Alkylation of iminosugars. To a mixture of the bromide chain (0.3 mmol, see Scheme 5A) and K_2CO_3 (0.4 mmol) was added a solution of the 5-hydroxymethyl nojirimycin derivative (0.2 mmol) in DMF (1 mL). The reaction suspension was stirred at 80 °C overnight. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified with HPLC.

***Figure 8**: Proton and carbon NMR numbering of N-alkylated iminosugars*



Synthesis of 5-*C*-hydroxymethyl-1-deoxynojirimycin (6)

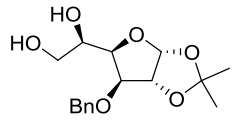
3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-furanoside (10):



BnBr (7.10 mL, 59.8 mmol) was added to a cooled (0 °C) and stirred mixture of diacetone-D-glucose (13.0 g, 49.9 mmol) and NaH (60% on mineral oil, 6.00 g, 150 mmol) in DMF (150 mL). After 18 h, TLC analysis showed complete conversion of starting material. Methanol was added to quench the excess NaH. The reaction mixture was diluted with water

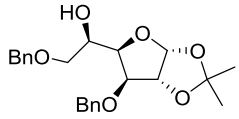
(250 mL) and extracted with Et_2O (3 x). The organic layers were combined and washed successively with sat. aq. $NaHCO_3$ and water, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography (4:1, PE:EtOAc) to give pure **10** (16.9 g, 48.2 mmol) in yield of 97% as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 5H, H_{Ar} Bn), 5.90 (d, *J* = 3.7 Hz, 1H, H-1), 4.72 – 4.55 (m, 3H, 2 x CH*H* Bn, H-2), 4.37 (dt, *J* = 7.8, 6.0 Hz, 1H, H-5), 4.16 – 4.10 (m, 2H, H-6a, H-4), 4.05 – 3.97 (m, 2H, H-6b, H-3), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (C_q Bn), 128.5, 128.0, 127.8 (CH_{Ar} Bn), 111.7, 108.9 (2 x C_q isopropyl), 105.2 (C-1), 82.6 (C-2), 81.6 (C-3), 81.3 (C-4), 72.5 (C-5), 72.3 (CH_2 Bn), 67.4 (C-6), 27.0, 26.9, 26.4, 25.6 (4 x CH_3).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanoside (11):



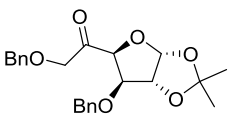
10 (14.0 g, 40.0 mmol) was dissolved in a mixture of acetic acid (45 mL) and water (20 mL), and the reaction mixture was stirred for 72 h at r.t. After TLC analysis showed complete consumption of starting material, ethyl acetate (100 mL) was added. The organic layer was washed successively with sat. aq. $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), filtrated and concentrated. The crude product was purified by silica gel column chromatography to gain **20** (9.92 g, 32.0 mmol) in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H, H_{Ar} Bn), 5.91 (dd, *J* = 3.9, 1.5 Hz, 1H, H-1), 4.70 (dd, *J* = 11.8, 1.9 Hz, 1H, CH*H* Bn), 4.60 (dd, *J* = 3.9, 1.5 Hz, 1H, H-2), 4.56 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.13 – 4.06 (m, 2H, H-3, H-4), 4.02 (dd, *J* = 8.9, 4.8 Hz, 1H, H-5), 3.79 (d, *J* = 11.0 Hz, 1H, H-6a), 3.67 (dd, *J* = 11.6, 5.5 Hz, 1H, H-6b), 1.47 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (C_q Bn), 128.7, 128.2, 127.9 (CH_{Ar} Bn), 111.9 (C_q isopropyl), 105.2 (C-1), 82.2 (C-2), 82.0 (C-3), 80.0 (C-4), 72.2 (C-5), 69.2 (CH_2 Bn), 64.7 (C-6), 26.8, 26.3 (2 x CH_3).

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-furanoside (12):



To a solution of **11** (8.29 g, 26.7 mmol) in toluene (250 mL) was added dibutyl tin oxide (10.0 g, 40.0 mmol). The reaction mixture was heated to reflux and stirred for 8 hours under Dean-Stark conditions. TBABr (1.03 g, 4.04 mmol) and benzyl bromide (6.36 mL, 53.6 mmol) were added to the solution. The reaction mixture was refluxed for another 18 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography (5:1 → 3:1, PE:EtOAc) to give **12** (9.61 g, 24.0 mmol, yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H, H_{Ar} Bn), 5.94 (d, *J* = 3.7 Hz, 1H, H-1), 4.68 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.59 – 4.47 (m, 3H, 3 x CH*H* Bn), 4.61 (d, *J* = 3.6 Hz, 1H, H-2), 4.21 – 4.15 (m, 2H, H-3, H-5), 4.11 (d, *J* = 1.9 Hz, 1H, H-4), 3.75 (d, *J* = 9.2 Hz, 1H, H-6a), 3.61 (d, *J* = 9.9 Hz, 1H, H-6b), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.3 (C_q Bn), 128.6, 128.5, 128.1, 127.8 (CH_{Ar} Bn), 111.8 (C_q isopropyl), 105.1 (C-1), 82.3 (C-2), 82.1 (C-4), 79.8 (C-3), 73.5 (CH_2 Bn), 72.4 (CH_2 Bn), 72.1 (C-6), 68.1 (C-5), 26.8, 26.3 (2 x CH_3).

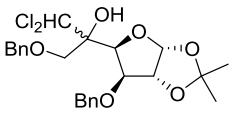
1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-α-D-*xylo*-hexofuranoside-5-ulose (13):



12 (8.62 g, 21.5 mmol) dissolved in dry DCM (100 mL) was added to a suspension of pyridinium chlorochromate (PCC, 15.34 g, 71.1 mmol) and activated 4 Å molecular sieves in dry DCM (300 mL). The reaction mixture was stirred under argon atmosphere at 30 °C overnight. 2-Propanol was then added to quench the reaction. Diethyl ether (200 mL) was added to dilute the dark brown suspension and the mixture was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel column chromatography and to give pure **13** (4.54 g, 11.40 mmol, yield 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.22 (m, 10H, H_{Ar} Bn), 6.05 (d, *J* = 3.6 Hz, 1H, H-1), 4.82 (d, *J* = 3.7 Hz, 1H, H-4), 4.62 (d, *J* = 3.6 Hz, 1H, H-2), 4.60 (d, *J* = 12.0, 1H, CH*H* Bn), 4.59 (d, *J* = 12.0 Hz, CH*H* Bn), 4.50 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.49 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.46 (d, *J* = 18.8 Hz, 1H, H-6a), 4.39 (d, *J* = 18.8 Hz, 1H, H-6b),

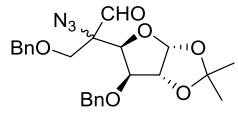
4.38 (d, *J* = 3.7 Hz, 1H, H-3), 1.49 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6 (C=O), 137.4, 136.7 (C_q Bn), 128.6, 128.5, 128.2, 127.9 (CH_{Ar} Bn), 112.5 (C_q isopropyl), 105.9 (C-1), 84.9 (C-4), 83.6 (C-3), 82.1 (C-2), 74.4 (C-6), 73.2, 72.6 (CH_2 Bn), 26.9, 26.3 (2 x CH_3).

1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-5-*C*-dichloromethyl-α-D-*gluco*/β-L-*ido*-furanoside (14):



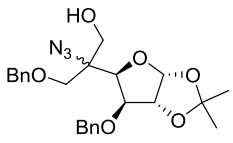
To a cooled (-78 °C) solution of LDA (36 mmol, 18 mL, 2 M in THF) in dry THF (45 mL) was added DCM (18 mL). After 30 minutes, **13** (4.48 g, 11.3 mmol) dissolved in DCM (18 mL) was added. After another 30 minutes temperature was allowed to rise to r.t. When TLC analysis indicated complete conversion of starting material, sat. aq. NH_4Cl was added. The mixture was extracted with EtOAc (100 mL) and the organic layer was washed successively with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (20:1 → 10:1, pentane:EtOAc) to gain **14** (3.00 g, 6.21 mmol, yield 55%), as a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.00 (m, 10H, H_{Ar} Bn), 6.11 (s, 1H, C*H*Cl_2), 5.89 (d, *J* = 3.9 Hz, 1H, H-1), 4.58 (d, *J* = 3.9 Hz, 1H, H-2), 4.56 – 4.43 (m, 5H, H-4, 2 x CH_2 Bn), 4.36 (d, *J* = 3.0 Hz, 1H, H-4), 3.94 (d, *J* = 10.0 Hz, 1H, H-6a), 3.85 (d, *J* = 10.0 Hz, 1H, H-6b), 1.41 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.9 (C_q Bn), 128.8 – 127.7 (CH_{Ar} Bn), 112.0 (C_q isopropyl), 103.7 (C-1), 84.9 (C-3), 81.5 (C-2), 79.7 (C-5), 75.8 (C-4), 73.8, 72.2 (CH_2 Bn), 72.2 (C-6), 26.7, 26.3 (2 x CH_3).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*gluco*/β-L-*ido*-furano-1,6-dialdose (15):



A mixture of **14** (2.69 g, 5.58 mmol), TBAI (1.07 g, 2.89 mmol) and NaN_3 (1.96 g, 30.0 mmol) in DMF (60 mL) was stirred at 115 °C for 18 h. After TLCMS analysis showed complete consumption of **14**, the reaction was quenched by the addition of water (100 mL) and extracted with EtOAc (75 mL x 3). The combined organic layers were washed with water (2 x) and brine (2 x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (10:1, pentane:EtOAc) to give **15** (1.74 g, 3.85 mmol, yield 69%). It is a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H, C*H*O), 7.47 – 7.30 (m, 10H, H_{Ar} Bn), 5.93 (d, *J* = 3.6 Hz, 1H, H-1), 4.67 – 4.41 (m, 5H, H-4, 2 x CH_2 Bn), 4.28 (d, *J* = 3.0 Hz, 1H, H-4), 4.08 (d, *J* = 10.2 Hz, 1H, H-6a), 4.05 (d, *J* = 3.0 Hz, 1H, H-3), 3.86 (d, *J* = 10.2 Hz, 1H, H-6b), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C=O), 137.2, 136.3 (C_q Bn), 128.6, 128.6, 128.3, 127.9, 127.6 (CH_{Ar} Bn), 112.3 (C-5), 105.2 (C-1), 81.9 (C-2), 81.4 (C-4), 81.1 (C-3), 73.7, 72.8 (2 x CH_2 Bn), 70.3 (C-6), 26.8, 26.2 (2 x CH_3).

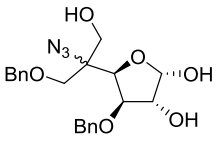
5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*gluco*/β-L-*ido*-furanoside (16):



$NaBH_4$ (0.33 g, 1.85 mmol) was added to a solution of **15** (1.68 g, 3.85 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, and quenched by the addition of sat. aq. NH_4Cl. The volatiles were evaporated. The residue was extracted with EtOAc (3 x). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography (20:1 → 10:1, pentane:EtOAc) to give **16** (1.56 g, 3.43 mmol, yield 89%), as a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 10H, H_{Ar} Bn), 5.91 (d, *J* = 3.8 Hz, 1H, H-1), 4.63 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.56 (d, *J* = 3.5 Hz, 1H, H-2), 4.52 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.47 (d, *J* = 12.4 Hz, 1H, CH*H* Bn), 4.30 (d, *J* = 3.2 Hz, 1H, CH*H* Bn), 4.02 (d, *J* = 3.2 Hz, 1H, H-3), 3.90 (d, *J* = 11.9 Hz, 1H, H-6a),

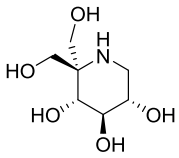
3.87 (d, *J* = 11.5 Hz, 1H, H-6b), 3.75 (d, *J* = 10.0 Hz, 1H, CH*H*OH), 3.67 (d, *J* = 10.1 Hz, 1H, CH*H*OH), 1.46 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.5 (C_q Bn), 128.6, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7 (CH_{Ar} Bn), 112.0 (C_q isopropyl), 104.4 (C-1), 82.2 (C-4), 81.7 (C-2), 80.0 (C-3), 73.6, 72.1 (CH_2 Bn), 71.2 (CH_2OH), 66.0 (C-5), 63.6 (C-6), 26.8, 26.3 (2 x CH_3).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-D-*gluco*/β-L-*ido*-furanoside (17):



16 (1.50 g, 3.29 mmol) was dissolved in a mixture of H_2O (15 mL) and TFA (15 mL) at 0 °C, the temperature was allowed to rise to r.t. and the mixture was stirred for 18 h. After TLC analysis indicated complete conversion of the starting material, TFA was removed by repetitive coevaporation with toluene. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (90 mL) and washed with brine (2 x). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography to give **17** (0.93 g, 2.24 mmol, yield 68%). It is a mixture of two inseparable diastereo-isomers at a ratio of 3:2. NMR data of the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 10H, H_{Ar} Bn), 5.47 (d, *J* = 4.6 Hz, 1H, H-1), 4.49 – 4.30 (m, 4H, 2 x CH_2 Bn), 4.21 (d, *J* = 2.8 Hz, 1H, H-3), 4.16 (dd, *J* = 4.0, 1.7 Hz, 1H, H-2), 3.99 (dd, *J* = 4.0, 1.6 Hz, 1H, H-4), 3.89 (d, *J* = 11.9 Hz, 1H, H-6a, 3.83 (d, *J* = 11.8 Hz, 1H, H-6b), 3.70 (d, *J* = 10.0 Hz, 1H, CH*H*OH), 3.67 (d, *J* = 10.2 Hz, 1H, CH*H*OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.0 (C_q Bn), 128.7, 128.5, 128.2, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 103.2 (C-1), 84.2 (C-4), 77.2 (C-3), 74.1 (C-2), 72.5, 71.9 (2 x CH_2 Bn), 70.4 (CH_2OH), 66.4 (C-5), 63.6 (C-6).

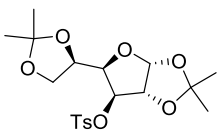
5-*C*-Hydroxymethyl-1-deoxynojirimycin (6):



Pd/C (10%, 0.28 g) was added to a solution of **17** (1.17 g, 2.82 mmol) in ethanol (50 mL) and pH of the solution was adjusted to 1 with 1M HCl. The reaction mixture was exposed to 5 bar of hydrogen and kept shaking for 24 hours. The reaction mixture was filtered over a pad of Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% → 20% methanol in DCM + 1% NH_4OH) to gain **6** as light yellow oil (0.40 g, 2.09 mmol, yield 74%). ^{1}H NMR (400 MHz, MeOD) δ 3.86 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.81 (d, *J* = 11.1 Hz, 1H, H-6a), 3.68 (d, *J* = 12.0 Hz, 1H, H-6*b), 3.67 (d, *J* = 11.1 Hz, 1H, H-6b), 3.64 (d, *J* = 9.6 Hz, 1H, H-4), 3.56 (dd, *J* = 9.2, 8.8 Hz, 1H, H-3), 3.58 – 3.51 (m, 1H, H-2), 3.07 (dd, *J* = 12.6, 4.6 Hz, 1H, H-1a), 2.86 – 2.78 (m, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 74.7 (C-3), 71.3 (C-4), 70.1 (C-2), 62.0 (C-5), 61.8 (C-6), 57.3 (C-6*), 43.7 (C-1). $[\alpha]^{20}_D$ = -0.3 (c = 0.54, MeOH). IR/cm^{-1}: 3277, 2926, 1612, 1450, 1406, 1259, 1076, 1039, 933. HRMS: found 194.10222 $[C_7H_{15}NO_5+H]^+$, calculated for $[C_7H_{15}NO_5+H]^+$ 194.10230.

Synthesis of 5-*C*-Hydroxymethyl-1-deoxy-D-galactonojirimycin (7)

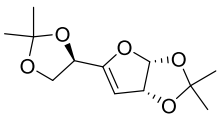
3-*O*-(*p*-Toluenesulfonyl)-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-furanoside (18):



p-Toluenesulfonyl chloride (3.60 g, 1.88 mmol) was added to a solution of diacetone-D-glucose (2.50 g, 8.61 mmol) in pyridine (24 mL) and DCM (24 mL). The reaction mixture was stirred overnight at a temperature of 60 °C. The volatiles were removed, and the residue was dissolved in DCM (30 mL), and the organic layer was washed with sat. aq. $NaHCO_3$, dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography to give **18** (3.50 g, 8.44 mmol, yield 98%). R_F = 0.41 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H, H_{Ar} Ts), 7.34 (d, *J* = 8.1 Hz, 2H, H_{Ar} Ts), 5.92 (d, *J* = 3.6 Hz, 1H, H-1), 4.83 (d, *J* = 3.7 Hz, 1H, H-2), 4.80 (d, *J* = 2.3 Hz, 1H, H-3), 4.07 – 3.96 (m, 3H, H-4, H-5, H-6a), 3.91 (dd, *J* = 8.2, 3.9 Hz, 1H, H-6b), 2.46 (s, 3H, CH_3 Ts), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 132.7, 130.2, 129.7, 128.4, 128.0 (C_{Ar} Ts), 112.5

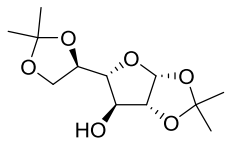
(C_q isopropyl), 109.1 (C_q isopropyl), 105.1 (C-1), 83.3 (C-2), 82.1 (C-3), 79.9 (C-4), 71.8 (C-5), 67.1 (C-6), 26.6, 26.2, 24.9, 21.7 (4 x CH_3), 14.2 (CH_3 Ts).

1,2:5,6-Di-*O*-isopropylidene-3-α-D-glucal (19):



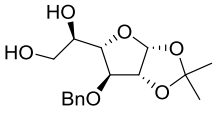
Potassium tert-butoxide (6.30 g, 10.1 mmol) was added to a solution of **18** (2.73 g, 6.59 mmol) in dried THF (40 mL) at 0 °C, and the mixture was stirred at 0 °C under argon atmosphere for 5 hours. Water (100 mL) was added and the reaction mixture was extracted with DCM (2 x 50 mL). The combined organic layers were washed successively with water and brine, dried (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel column chromatography (5:1, PE:EtOAc) to give **19** (1.45 g, 5.99 mmol, yield 91%). R_F = 0.78 (5:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, *J* = 5.2 Hz, 1H, H-1), 5.31 (ddd, *J* = 5.3, 2.3, 1.5 Hz, 1H, H-2), 5.26 (dd, *J* = 2.4, 1.2 Hz, 1H, H-3), 4.60 (dd, *J* = 7.0, 5.6 Hz, 1H, H-5), 4.17 (d, *J* = 8.4 Hz, 1H, H-6a), 3.99 (d, *J* = 8.5 Hz, 1H, H-6b), 1.48 (s, 6H, 2 x CH_3), 1.45 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C-4), 112.3 (C_q isopropyl), 110.3 (C_q isopropyl), 106.6 (C-1), 99.0 (C-3), 83.4 (C-2), 71.3 (C-5), 67.0 (C-6), 28.2, 27.9, 26.2, 25.5 (4 x CH_3).

1,2:5,6-Di-*O*-isopropylidene-α-D-*galacto*-furanoside (20):



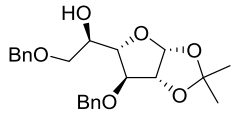
To a solution of **19** (0.49 g, 2.02 mmol) in THF (3 mL) was added BH_3·THF complex (1M, 2.5 mL, 2.5 mmol) at 0 °C under argon atmosphere. After 4 hours a mixture of aq. NaOH (2M, 0.9 mL) and 30% H_2O_2 (0.4 mL) was added to the reaction mixture. The reaction was stirred at r.t. for 1 hour, and the volatiles were evaporated. The residue was diluted with water (5 mL), and the water layer extracted with EtOAc (4 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The crude product was crystallized from EtOAc and pentane to give **20** as a crystalline product (0.40 g, 1.53 mmol, 75%). R_F = 0.24 (5:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.9 Hz, 1H, H-1), 4.55 (dd, *J* = 3.9, 1.4 Hz, 1H, H-2), 4.37 (q, *J* = 6.8 Hz, 1H, H-5), 4.13 (dd, *J* = 4.5, 1.3 Hz, 1H, H-3), 4.08 (dd, *J* = 8.4, 6.6 Hz, 1H, H-6a), 3.88 (d, *J* = 6.8 Hz, 1H, H-4), 3.86 (dd, *J* = 8.0, 7.0 Hz, 1H, H-6b), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.8, 110.0 (2 x C_q isopropyl), 105.1 (C-1), 87.7 (C-2), 86.0 (C-4), 76.3 (C-3), 75.5 (C-4), 65.8 (C-6), 27.6, 26.9, 26.7, 25.4 (4 x CH_3).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*galacto*-furanoside (22):



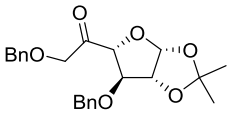
To a solution of **20** (4.00 g, 15.4 mmol) in DMF (150 mL) at 0 °C under argon atmosphere, was added NaH (60% mineral oil, 1.85 g, 46.3 mmol). After 30 minutes, BnBr (40 mL, 33.7 mmol) was added. The reaction mixture was stirred at r.t. overnight. The excess NaH was quenched by the addition of methanol, and the volatiles were evaporated. The residue was dissolved in DCM, washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The crude product **21** (R_F = 0.18, 5:3, PE:EtOAc) was dissolved in water (10 mL) and AcOH (60 mL). The reaction mixture was stirred at r.t. overnight. The volatiles were evaporated, and the residue was purified by silica gel column chromatography (3:2 → 1:1, PE:EtOAc) to give **22** (4.12 g, 13.2 mmol, 86% yield over the 2 steps). R_F = 0.82 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H, H_{Ar} Bn), 5.92 (d, *J* = 4.1 Hz, 1H, H-1), 4.69 (dd, *J* = 4.1, 1.1 Hz, 1H, H-2), 4.65 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.57 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.14 (dd, *J* = 6.7, 3.5 Hz, 1H, H-4), 4.01 (dd, *J* = 3.5, 1.1 Hz, 1H, H-3), 3.80 (ddd, *J* = 6.7, 4.8, 3.8 Hz, 1H, H-5), 3.70 (dd, *J* = 11.8, 3.8 Hz, 1H, H-6a), 3.59 (dd, *J* = 11.7, 4.8 Hz, 1H, H-6b), 1.53 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C_q Bn), 128.7, 128.3, 128.0 (CH_{Ar} Bn), 113.3 (C_q isopropyl), 105.7 (C-1), 85.4 (C-2), 85.4 (C-4), 83.1 (C-3), 72.0 (CH_2 Bn), 70.9 (C-5), 63.9 (C-6), 27.2, 26.5 (2 x CH_3).

3,6-Di-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*galacto*-furanoside (23):



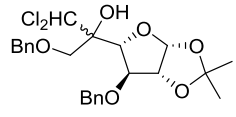
23 was synthesized from **22** (3.30 g, 10.6 mmol) in a yield of 82% (3.49 g, 8.72 mmol), as a thick yellow oil, as described for the synthesis of **12**. R_F = 0.80 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 10H, H_{Ar} Bn), 5.95 (d, *J* = 4.2 Hz, 1H, H-1), 4.71 (d, *J* = 3.9 Hz, 1H, H-2), 4.61 (d, *J* = 11.4 Hz, 1H, CH*H* Bn), 4.57 (s, 2H, CH_2 Bn), 4.54 (d, *J* = 11.7 Hz, 1H, CH*H* Bn)), 4.19 (dd, *J* = 6.5, 3.4 Hz, 1H, H-4), 4.12 (dd, *J* = 3.4, 1.1 Hz, 1H, H-3), 3.98 (q, *J* = 5.8 Hz, 1H, H-5), 3.59 (dd, *J* = 9.9, 5.7 Hz, 1H, H-6a), 3.55 (dd, *J* = 9.9, 5.3 Hz, 1H, H-6b), 1.57 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.2 (C_q Bn), 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.8, 127.8 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 105.5 (C-1), 85.6 (C-2), 85.2 (C-4), 83.1 (C-3), 73.6 (CH_2 Bn), 71.9 (CH_2 Bn), 71.4 (C-6), 69.7 (C-5), 27.1, 26.4 (2 x CH_3).

3,6-Di-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*arabino*-hexofuranoside-5-ulose (24):



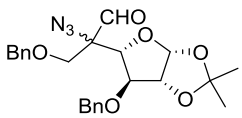
24 was synthesized from **23** (3.50 g, 8.74 mmol) in a yield of 92% (3.20 g, 8.04 mmol), as a thick yellow oil, as described for the synthesis of **13**. R_F = 0.67 (10:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H, H_{Ar} Bn), 5.98 (d, *J* = 3.8 Hz, 1H, H-1), 4.70 (d, *J* = 18.4 Hz, 1H, CH*H* Bn), 4.65 – 4.61 (m, 3H, H-2, H-3, CH*H* Bn), 4.60 – 4.56 (m, 3H, H_2-6, CH*H* Bn), 4.52 (d, *J* = 1.0 Hz, 1H, H-4), 4.37 (d, *J* = 18.4 Hz, 1H, CH*H* Bn), 1.31 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (C-5), 137.2 – 127.8 (C_{Ar} Bn), 112.3 (C_q isopropyl), 106.5 (C-1), 88.6 (C-2), 83.6 (C-4), 83.5 (C-3), 73.4 (CH_2 Bn), 73.1 (CH_2 Bn), 72.0 (C-6), 25.7, 25.6 (2 x CH_3).

1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-5-*C*-dichloroemethyl-α-D-*galacto*/β-L-*altro*-furanoside (25):



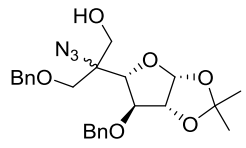
25 was synthesized from **24** (3.20 g, 8.03 mmol) in a yield of 74% (2.87 g, 5.94 mmol) as a thick yellow oil as described for the synthesis of **14**. R_F = 0.52 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 10H, H_{Ar} Bn), 5.95 – 5.93 (m, 1H, $CHCl_2$), 5.80 (dd, *J* = 3.9, 1.6 Hz, 1H, H-1), 4.66 (d, *J* = 11.6, 1H, CH*H* Bn), 4.63 (dd, *J* = 3.8, 1.4 Hz, 1H, H-2), 4.60 (d, *J* = 11.6, 1H, CH*H* Bn), 4.56 (d, *J* = 1.7 Hz, 2H, CH_2 Bn), 4.50 – 4.46 (m, 1H, H-3), 4.44 – 4.38 (m, 1H, H-4), 3.81 (m, 2H, H_2-6), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 – 127.8 (C_{Ar} Bn), 114.1 (C_q isopropyl), 104.8 (C-1), 85.2 (C-2), 84.8 (C-4), 81.7 (C-3), 76.6 (C-5), 75.7 ($CHCl_2$), 73.8 (CH_2 Bn), 72.3 (CH_2 Bn), 70.1 (C-6), 27.2, 26.7 (2 x CH_3). HRMS: found 505.11521 $[C_{24}H_{28}Cl_2O_6+Na]^+$, calculated for $[C_{24}H_{28}Cl_2O_6+Na]^+$ 505.11552.

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*galacto*/β-L-*altro*-furano-1,6-dialdose (26):



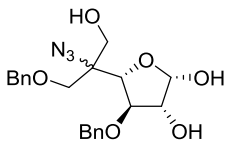
26 was synthesized from **25** (2.90 g, 6.00 mmol) in a yield of 93% as a thick yellow oil as described for the synthesis of **15**. R_F = 0.52 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H, CHO), 7.54 – 7.19 (m, 10H, H_{Ar} Bn), 5.75 (d, *J* = 4.0 Hz, 1H, H-1), 4.69 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.64 (dd, *J* = 4.0, 1.5 Hz, 1H, H-2), 4.54 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.52 (d, *J* = 4.1 Hz, 2H, CH_2 Bn), 4.14 (dd, *J* = 6.3, 1.5 Hz, 1H, H-3), 4.11 (d, *J* = 6.3 Hz, 1H, H-4), 3.96 (d, *J* = 10.0 Hz, 1H, H-6a), 3.60 (d, *J* = 10.0 Hz, 1H, H-6b), 1.61 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (CHO), 136.9, 136.7 (C_q Bn), 128.5, 128.2, 128.1, 128.0, 127.7 (CH_{Ar} Bn), 115.1 (C_q isopropyl), 104.6 (C-1), 85.4 (C-2), 82.0 (C-3), 81.9 (C-4), 73.8 (CH_2 Bn), 72.4 (CH_2 Bn), 70.8 (C-5), 70.5 (C-6), 27.5, 27.1 (2 x CH_3). HRMS: found 476.17913 $[C_{24}H_{27}N_3O_6+Na]^+$, calculated for $[C_{24}H_{27}N_3O_6+Na]^+$ 476.19721.

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*galacto*/β-L-*altro*-furanoside (27):



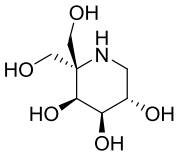
27 was synthesized from **26** (2.50 g, 5.51 mmol) in a yield of 82% (2.06 g, 4.52 mmol), as thick yellow oil, as described for the synthesis of **16**. R_F = 0.22 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.18 (m, 10H, H_{Ar} Bn), 5.76 (d, *J* = 4.0 Hz, 1H, H-1), 4.67 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.62 (dd, *J* = 4.1, 1.5 Hz, 1H, H-2), 4.50 (d, *J* = 12.0, 1H, CH*H* Bn), 4.49 (s, 2H, CH_2OH), 4.22 (dd, *J* = 6.4, 1.5 Hz, 1H, H-3), 3.99 (d, *J* = 12.0 Hz, 1H, H-6a), 3.95 (d, *J* = 6.4 Hz, 1H, H-4), 3.93 (d, *J* = 11.9 Hz, 1H, H-6b), 4.04 – 3.86 (m, 3H, H-4, H_2-6), 3.61 (d, *J* = 9.9 Hz, 1H, CH*H* Bn), 3.52 (d, *J* = 10.0 Hz, 1H, CH*H* Bn), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 – 127.9 (C_{Ar} Bn), 115.2 (C_q isopropyl), 104.7 (C-1), 86.1 (C-2), 83.4 (C-4), 82.4 (C-3), 74.0 (CH_2OH), 72.7 (CH_2 Bn), 71.4 (CH_2 Bn), 66.1 (C-5), 63.9 (C-6), 27.8, 27.4 (2 x CH_3). HRMS: found 478.19451 $[C_{24}H_{29}N_3O_6+Na]^+$, calculated for $[C_{24}H_{29}N_3O_6+Na]^+$ 478.19486.

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-α-D-*galacto*/β-L-*altro*-furanoside (28):



28 was synthesized from **27** (2.08 g, 4.57 mmol) in a yield of 63% (1.31 g, 2.88 mmol), as a thick yellow oil, as described for the synthesis of **17**. **28** was obtained as an inseparable mixture of diastereo isomers (ratio 1:0.9). NMR data of the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, *J* = 3.9 Hz, 1H, H-1), 4.61 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.45 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.43 (s, 2H, C*H*$_2$OH), 4.07 (d, *J* = 3.8 Hz, 1H, H-3), 4.03 (t, *J* = 4.0 Hz, 1H, H-2), 3.93 (dd, *J* = 11.8, 4.7 Hz, 1H, H-6a), 3.89 (d, *J* = 5.3 Hz, 1H, H-4), 3.85 (d, *J* = 11.8 Hz, 1H, H-6b), 3.59 (d, *J* = 10.1 Hz, 1H, CH*H* Bn), 3.42 (d, *J* = 10.0 Hz, 1H, CH*H* Bn). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.4 (C_q Bn), 128.7, 128.7, 128.4, 128.4, 128.2, 128.2, 127.8, 127.8 (CH_{Ar} Bn), 97.1 (C-1), 84.0 (C-3), 81.3 (C-4), 76.0 (C-2), 73.9 (CH_2OH), 72.1 (CH_2 Bn), 71.1 (CH_2 Bn), 66.5 (C-5), 62.4 (C-6). HRMS: found 438.16347 $[M+Na]^+$, calculated for $[+Na]^+$ 438.19486.

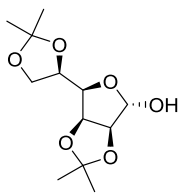
5-*C*-Hydroxymethyl-1-deoxy-D-galactonojirimycin (7):



7 was synthesized from **28** (1.00 g, 2.42 mmol) in a yield of 91% (0.42 g, 2.20 mmol), as thick yellow oil, as described for the synthesis of **6**. R_F = 0.26 (1% NH_4OH in MeOH). ^{1}H NMR (400 MHz, MeOD) δ 3.99 (d, *J* = 3.3 Hz, 1H, H-4), 3.87 (d, *J* = 11.3 Hz, 1H, H-6a), 3.83 (td, *J* = 7.8, 4.3 Hz, 1H, H-2), 3.75 (d, *J* = 11.4 Hz, 1H, H-6*a), 3.71 (dd, *J* = 7.6, 3.3 Hz, 1H, H-3), 3.68 (d, *J* = 11.2 Hz, 1H, H-6b), 3.63 (d, *J* = 11.3 Hz, 1H, H-6*b), 3.13 (dd, *J* = 13.2, 4.3 Hz, 1H, H-1a), 2.71 (dd, *J* = 13.2, 7.9 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 72.0 (C-3), 68.4 (C-4), 68.3 (C-2), 61.9 (C-6), 60.9 (C-5), 59.7 (C-6*), 43.6 (C-1). $[\alpha]^{20}_D$ = +0.8 (c = 0.57, MeOH). IR/cm^{-1}: 3275, 2922, 2497, 1608, 1049, 1338, 1247, 1114, 1056, 1024. HRMS: found $[C_7H_{15}NO_5+H]^+$ 194.10221, calculated for $[C_7H_{15}NO_5+H]^+$ 194.10230.

Synthesis of 5-*C*-hydroxymethyl-1-deoxy-D-mannonojirimycin (8)

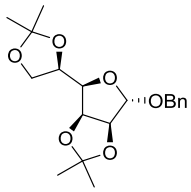
2,3:5,6-Di-*O*-isopropyl-α-D-*manno*-furanoside (29):



To a solution of D-mannose (36.0 g, 180 mmol) in dry acetone (1000 mL) at r.t. was added tetrabutylammonium tribromide (TBATB, 1.97 g, 4.08 mmol).[6] The reaction was monitored by TLC analysis. After complete conversion of the starting material, acetone was removed on a rotary evaporator. Title compound **29** was isolated by crystallization (3:1, pentane:EtOAc, 30.2 g, 116 mmol, yield 64%). R_F = 0.40 (10:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, *J* = 2.7 Hz, 1H, H-1), 4.80 (dd, *J* = 5.9, 3.7 Hz, 1H, H-3), 4.60 (d, *J* = 5.9 Hz, 1H, H-2), 4.40 (q, *J* = 4.0 Hz, 1H, H-5), 4.16 (dd, *J* = 7.2, 3.6 Hz, 1H, H-4), 4.07 (d, *J* = 5.9 Hz, 2H, H-6a, H-6b), 1.46 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR

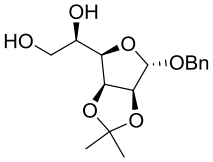
(100 MHz, $CDCl_3$) δ 112.3, 108.9 (2 x C_q isopropyl), 100.8 (C-1), 85.3 (C-2), 79.7 (C-4), 79.4 (C-3), 73.1 (C-5), 66.2 (C-6), 26.5, 25.6, 24.9, 24.2 (4 x CH_3).

Benzyl-2,3:5,6-di-*O*-isopropyl-α-D-*manno*-furanoside (30):



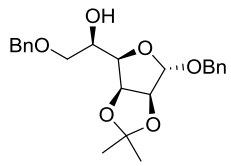
To a solution of **29** (1.28 g, 4.92 mmol) in THF (10 mL) was successively added freshly powdered potassium hydroxide (0.48 g, 8.56 mmol), 18-crown-6 (0.055 g, 0.21 mmol) and benzyl bromide (0.67 mL, 0.96 g, 5.64 mmol). The mixture was stirred at r.t. and the reaction was monitored by TLC analysis. After complete conversion of the starting material, the mixture was diluted with DCM and washed with water (3 x). The organic layer was dried (Na_2SO_4), filtered and concentrated, and the residue was purified by silica gel column chromatography (9:1, PE:EtOAc) to gain **30** (1.29 g, 3.68 mmol, yield 75%), R_F = 0. 70 (6:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H, H_{Ar} Bn), 5.08 (s, 1H, H-1), 4.80 (dd, *J* = 5.9, 3.6 Hz, 1H, H-3), 4.67 (d, *J* = 5.9 Hz, 1H, H-2), 4.64 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.49 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.11 (ddd, *J* = 7.9, 6.3, 4.3 Hz, 1H, H-5), 4.14 (dd, *J* = 8.7, 6.3 Hz, 1H, H-6a), 4.02 (dd, *J* = 8.8, 4.4 Hz, 1H, H-6b), 4.00 (dd, *J* = 8.0, 3.6 Hz, 1H, H-4), 1.46 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4 (C_q Bn), 128.6 – 127.9 (CH_{Ar} Bn), 112.7, 109.4 (2 x C_q isopropyl), 105.7 (C-1), 85.2 (C-2), 80.5 (C-4), 79.7 (C-3), 73.2 (C-5), 69.3 (CH_2 Bn), 67.1 (C-6), 27.1, 26.0, 25.3, 24.6 (4 x CH_3).

Benzyl-2,3-*O*-isopropyl-α-D-*manno*-furanoside (31):



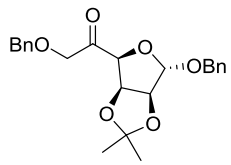
31 was synthesized from **30** (15.00 g, 42.84 mmol) in a yield of 81% (10.8 g, 34.8 mmol) as described for the synthesis of **11**. R_F = 0.19 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, H_{Ar} Bn), 5.10 (s, 1H, H-1), 4.85 (dd, *J* = 5.9, 3.6 Hz, 1H, H-3), 4.65 (d, *J* = 6.0 Hz, 1H, H-2), 4.62 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.48 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.05 – 3.98 (m, 1H, H-5), 3.95 (dd, *J* = 8.3, 3.6 Hz, 1H, H-4), 3.82 (dd, *J* = 11.5, 3.2 Hz, 1H, H-6a), 3.65 (dd, *J* = 11.5, 5.9 Hz, 1H, H-6b), 3.28 (s, 1H, OH), 2.96 (s, 1H, OH), 1.46 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (C_q Bn), 128.4, 128.0, 127.8 (CH_{Ar} Bn), 112.6 (C_q isopropyl), 105.3 (C-1), 84.7 (C-2), 80.0 (C-3), 79.2 (C-4), 70.1 (C-5), 69.1 (CH_2 Bn), 64.3 (C-6), 28.8, 24.5 (2 x CH_3).

Benzyl-2,3-*O*-isopropyl-6-*O*-benzyl-α-D-*manno*-furanoside (32):



32 was synthesized from **31** (10.7 g, 34.4 mmol) in a yield of 76% (10.5 g, 26.2 mmol) as thick yellow oil, as described for the synthesis of **12**. R_F = 0.64 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H, 2 x H_{Ar} Bn), 5.09 (s, 1H, H-1), 4.87 (dd, *J* = 5.9, 3.7 Hz, 1H, H-3), 4.65 (d, *J* = 5.9 Hz, 1H, H-2), 4.64 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.62 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.58 (d, *J*= 11.9 Hz 1H, CH*H* Bn), 4.44 (d, *J*= 11.7 Hz 1H, CH*H* Bn), 4.15 (ddd, *J* = 8.4, 5.8, 3.3 Hz, 1H, H-5), 4.03 (dd, *J* = 8.3, 3.6 Hz, 1H, H-4), 3.73 (dd, *J* = 9.8, 3.3 Hz, 1H, H-6a), 3.63 (dd, *J* = 9.8, 5.7 Hz, 1H, H-6b), 1.47 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.4 (2 x C_q Bn), 128.6 – 127.8 (CH_{Ar} Bn), 112.7 (C_q isopropyl), 105.4 (C-1), 85.0 (C-2), 80.2 (C-3), 79.1 (C-4), 73.6 (CH_2 Bn), 71.9 (C-6), 69.1 (CH_2 Bn), 69.0(C-5), 26.1, 24.7(2 x CH_3).

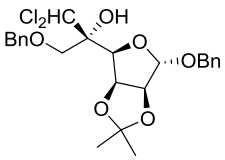
Benzyl-2,3-*O*-isopropyl-6-*O*-benzyl-α-D-lyxo-hexofuranoside-5-ulose (33):



33 (4.21 g, 10.5 mmol) was synthesized from **32** in a yield of 88% (3.66 g, 9.18 mmol), as described for the synthesis of **13**. R_F = 0.63 (3:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 10H, H_{Ar} Bn), 5.23 (s, 1H, H-1), 5.11 (dd, *J* = 5.8, 4.2 Hz, 1H, H-3), 4.73 (d, *J* = 4.2 Hz, 1H, H-4), 4.67 (d, *J* = 11.6 Hz, CH*H* Bn), 4.65 (d, *J* = 11.6 Hz, CH*H* Bn), 4.64 (d, *J* = 5.8 Hz, 1H, H-2), 4.61 (d, *J* = 11.6 Hz, CH*H* Bn), 4.49 (d, *J* = 11.6 Hz, CH*H* Bn),

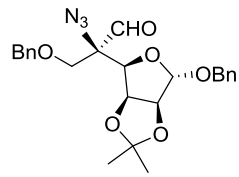
4.35 (s, 2H, H_2-6), 1.35 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (C=O), 137.2, 136.8 (2 x C_q Bn), 128.6 – 128.0 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 105.4 (C-1), 84.3 (C-2), 84.2 (C-4), 80.7 (C-3), 74.1, 73.4 (2 x CH_2 Bn), 69.3 (C-6), 25.7, 24.5 (2 x CH_3).

Benzyl-2,3-*O*-isopropyl-6-*O*-benzyl-5-*C*-dichloromethyl-β-L-*gulo*-furanoside (34):



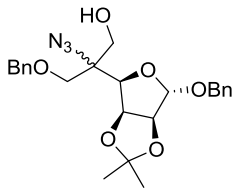
34 was synthesized from **33** in a yield of 66% (3.90 g, 8.34 mmol) as described for the synthesis of **14**. R_F = 0.53 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.15 (m, 10H, H_{Ar} Bn), 6.19 (s, 1H, C*H*Cl_2), 5.17 (s, 1H, H-1), 5.05 (dd, *J* = 5.9, 3.4 Hz, 1H, H-3), 4.87 (s, 1H, -OH), 4.71 – 4.57 (m, 4H, H-4, 3 x CH*H* Bn), 4.39 (d, *J* = 11.4 Hz, 1H, CH*H* Bn), 4.28 (d, *J* = 3.4 Hz, 1H, H-2), 3.76 (d, *J* = 9.8 Hz, 1H, H-6a), 3.61 (d, *J* = 9.8 Hz, 1H, H-6b), 1.51 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 – 127.8 (C_{Ar} Bn), 113.3 (C_q isopropyl), 105.0 (C-1), 85.0 (C-4), 81.7 (C-3), 77.9 (C-2), 73.9 (CH_2 Bn), 73.3 ($CHCl_2$), 70.8 (C-5), 69.1 (C-6), 25.8, 24.2 (2 x CH_3).

Benzyl-5-deoxy-5-azido-5-*C*-benzyloxymethyl-2,3-*O*-isopropylidene-α-D-*manno*-furano-1,6-dialdose (35):



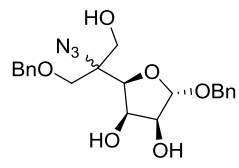
35 was synthesized from **34** (2.82 g, 5.84 mmol) in a yield of 87% (2.30 g, 5.07 mmol), as described for the synthesis of **15**. R_F = 0.52 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H, CHO), 7.39 – 7.28 (m, 10H, H_{Ar} Bn), 5.18 (s, 1H, H-1), 4.84 (dd, *J* = 5.9, 3.4 Hz, 1H, H-3), 4.70 – 4.60 (m, 4H, H-4, 3 x CH*H* Bn), 4.51 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.29 (d, *J* = 3.4 Hz, 1H, H-2), 3.90 (d, *J* = 10.2 Hz, 1H, H-6a), 3.82 (d, *J* = 10.2 Hz, 1H, H-6b), 1.45 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8 (CHO), 137.2 (C_q Bn), 128.6 – 127.7 (CH_{Ar} Bn), 113.3 (C_q isopropyl), 105.6 (C-1), 84.6 (C-4), 80.4 (C-2), 79.2 (C-3), 73.9 (CH_2 Bn), 70.5 ($C_q CN_3$), 69.9 (C-6), 69.5 (CH_2 Bn), 25.3, 24.2 (2 x CH_3).

Benzyl-5-deoxy-5-azido-5-*C*-benzyloxymethyl-2,3-*O*-isopropyl-α-D-*manno*/β-L-*gulo*-furanoside (36):



36 was synthesized from **35** (0.37 g, 0.82 mmol) in a yield of 80% (0.30 g, 0.65 mmol) as two inseparable diastereomers as described for the synthesis of **16**. R_F = 0.22 (9:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 10H, CH_{Ar} Bn), 5.09 (s, 1H, H-1), 4.77 (dd, *J* = 5.8, 3.3 Hz, 1H, H-3), 4.64 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.63 (d, *J* = 5.8 Hz, H-4), 4.62 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.55 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.45 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.23 (d, *J* = 3.2 Hz, 1H, H-2), 3.91 (d, *J* = 2.1 Hz, 2H, C*H*$_2$OH), 3.87 (d, *J* = 10.1 Hz, 1H, H-6a), 3.78 (d, *J* = 10.1 Hz, 1H, H-6b), 1.45 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.4 (C_q Bn), 128.5 – 127.7 (CH_{Ar} Bn), 112.9 (C_q isopropyl), 104.8 (C-1), 85.1(C-4), 79.8 (C-2), 79. 5 (C-3), 73.8 (CH_2 Bn), 70.9 (C-6), 69.3 (CH_2 Bn), 66.6 ($C_q N_3$), 63.7 (CH_2OH), 25.7, 24.3 (2 x CH_3).

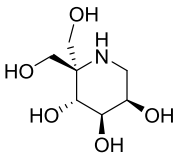
Benzyl-5-deoxy-5-azido-5-*C*-benzyloxymethyl-α-D-manno/β-L-*gulo*-furanoside (37):



36 (0.19 g, 0.43 mmol) was dissolved in a mixture of H_2O (0.6 mL) and TFA (1.8 mL) at 0 °C, the temperature was allowed to rise to r.t. and the mixture was stirred for 18 h. After TLC analysis indicated complete conversion of the starting material, the reaction mixture was diluted with water (5 mL), extracted with EtOAc (20 mL) and washed with brine (2 x). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography to give **37** (0.08 g, 0.19 mmol, yield 45%). R_F = 0.16 (5:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 10H, CH_{Ar} Bn), 5.09 (d, *J* = 2.2 Hz, 1H, H-1), 4.66 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.60 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.57 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.55 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.33 (ddd, *J* = 5.1,

4.1, 1.0 Hz, 1H, H-3), 4.14 (dd, *J* = 2.3, 5.3 Hz, 1H, H-2), 4.13 (dd, *J* = 4.0, 0.8 Hz, 1H, H-4), 3.94 (d, *J* = 11.6 Hz, 1H, H-6a), 3.84 (dd, *J* = 11.7, 0.8 Hz, 1H, H-6b), 3.75 (s, 2H, C*H*$_2$OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.8 (C_q Bn), 128.7 – 127.8 (CH_{Ar} Bn), 107.2 (C-1), 79.7 (C-4), 77.1 (C-2), 74.0 (CH_2 Bn), 71.6 (C-3), 70.4 (CH_2 Bn), 70.2 (CH_2OH), 66.8 (C-5), 63.8 (C-6).

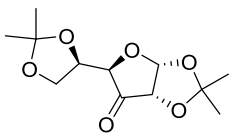
5-*C*-Hydroxymethyl-1-deoxy-D-mannonojirimycin (8):



8 was synthesized from **37** (0.83 g, 2.0 mmol) in a yield of 82% (0.32 g, 1.64 mmol) as described for the synthesis of **6**. ^{1}H NMR (400 MHz, MeOD) δ 4.17 (ddd, *J* = 1.5, 3.0, 3.7 Hz, 1H, H-2), 4.10 (d, *J* = 9.2 Hz, 1H, H-4), 3.95 (d, *J* = 11.6 Hz, 1H, H-6a), 3.94 (d, *J* = 12.6 Hz, 1H, H-6a'), 3.86 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3), 3.77 (d, *J* = 11.6 Hz, 1H, H-6b), 3.71 (d, *J* = 12.5 Hz, 1H, H-6b'), 3.40 (dd, *J* = 1.5, 13.2 Hz, 1H, H-1a), 3.28 (dd, *J* = 3.7, 13.1 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 71.9 (C-3), 68.5 (C-4), 67.8 (C-2), 67.0 (C-5), 61.6 (C-6), 58.5 (C-6'), 45.7 (C-1). IR/cm^{-1}: 3307, 1636, 1451, 1229, 1073. HRMS: found 194.10223 $[C_7H_{15}NO_5+H]^+$, calculated for $[C_7H_{15}NO_5+H]^+$ 194.10230.

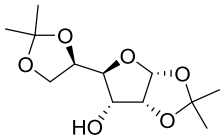
Synthesis of 5-*C*-hydroxymethyl-1-deoxy-D-allonojirimycin (9)

1,2:5,6-Di-*O*-isopropylidene-α-D-*allo*-furanoside-3-ulose (38):



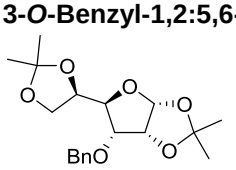
To a mixture of diacetone-D-glucose (15.0 g, 57.7 mmol) in anhydrous DCM (350 mL) and activated 4Å molecular sieves at 0 °C, was added pyridinium chlorochromate (PCC, 24.3 g, 112 mmol). The reaction mixture was stirred at r.t. overnight under argon atmosphere. The dark brown mixture was then filtered through a pad of silica gel, and the silica gel pad was rinsed with EtOAc (2 x 200 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (5:1 → 2:1, PE:EtOAc) to gain **38** (12.1 g, 47.0 mmol, yield 81%), R_F = 0.2 (19:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, *J* = 4.5 Hz, 1H, H-1), 4.41 (d, *J* = 4.6 Hz, 1H, H-2), 4.38 (d, *J* = 0.7 Hz, 1H, H-4), 4.37 (td, *J* = 2.5, 0.6 Hz, 1H, H-5), 4.06 (d, *J* = 0.7 Hz, 1H, H-6a), 4.05 – 4.03 (m, 1H, H-6b), 1.48 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.36 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9 (C=O), 114.3 (C_q isopropyl), 110.4 (C_q isopropyl), 103.1 (C-1), 78.9 (C-4), 77.2 (C-2), 76.4 (C-5), 64.3 (C-6), 27.6, 27.2, 26.0, 25.3 (4 x CH_3).

1,2:5,6-Di-*O*-isopropylidene-α-D-*allo*-furanoside (39):



38 (12.1 g, 47.0 mmol) was dissolved in a mixture of water and ethanol (72 mL, 4:5). In small portions $NaBH_4$ (8.70 g, 230 mmol) was added. After stirred for 7 hours, the reaction mixture was extracted with DCM (3 x). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel column chromatography (5:1 → 3:2, PE:EtOAc), to give **39** (11.2 g, 43.1 mmol, yield 92%). R_F = 0.4 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, *J* = 3.8 Hz, 1H, H-1), 4.62 (dd, *J* = 5.2, 3.8 Hz, 1H, H-2), 4.31 (td, *J* = 6.6, 4.7 Hz, 1H, H-5), 4.09 (dd, *J* = 8.5, 6.6 Hz, 1H, H-6a), 4.02 (dd, *J* = 8.5, 6.6 Hz, 1H, H-6b), 3.82 (dd, *J* = 8.5, 4.7 Hz, 1H, H-4), 2.55 (br s, 1H, -OH), 1.58 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.38 (d, *J* = 5.2 Hz, 6H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.0 (C_q isopropyl), 110.0 (C_q isopropyl), 104.1 (C-1), 79.9 (C-4), 79.1 (C-2), 75.7 (C-5), 72.7 (C-3), 66.0 (C-6), 26.7, 26.7, 26.5, 25.4 (4 x CH_3).

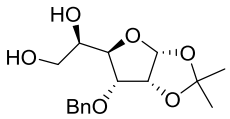
3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-furanoside (40):



NaH (60% on mineral oil, 0.042 g, 1.05 mmol) was added to a solution of **39** (0.14 g, 0.54 mmol) in DMF (2 mL) at 0 °C under argon atmosphere. The mixture was stirred for 1 hour, subsequently, BnBr (0.1 mL, 0.84 mmol) was added. The suspension was stirred overnight at r.t. The

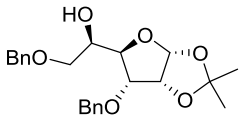
reaction was quenched by the addition of methanol (3 mL), and volatiles were evaporated. The residue was dissolved with EtOAc (10 mL), washed with brine (3 x), dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography to give **40** (0.17 g, 0.48 mmol, yield 90%). R_F = 0.8 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, *J* = 3.7 Hz, 1H, H-1), 4.78 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.60 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.59 (t, *J* = 4.2 Hz, 1H, H-2), 4.37 (td, *J* = 7.0, 3.2 Hz, 1H, H-5), 4.15 (dd, *J* = 8.7, 3.2 Hz, 1H, H-4), 4.02 (dd, *J* = 8.3, 6.9 Hz, 1H, H-6a), 3.97 (dd, *J* = 8.3, 7.1 Hz, 1H, H-6b), 3.90 (d, *J* = 4.5 Hz, 1H, H-3), 1.60 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.37 (s, 4H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (C_q Bn), 128.4, 128.2, 128.0 (CH_{Ar} Bn), 112.9 (C_q isopropyl), 109.6 (C_q isopropyl), 103.9 (H-1), 78.0 (C-4), 77.8 (C-2), 77.5 (C-3), 74.8 (C-5), 72.2 (CH_2 Bn), 65.0 (C-6), 26.8, 26.6, 26.2, 25.1 (4 x CH_3).

3-*O*-Benzyl-1,2-di-*O*-isopropylidene-α-D-*allo*-furanoside (41):



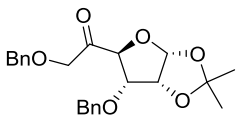
41 was synthesized from **40** (9.0 g, 25.68 mmol) in a yield of 46% (3.67 g, 11.8 mmol), as described for the synthesis of **11**. R_F = 0.15 (1:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H, H_{Ar} Bn), 5.79 (d, *J* = 3.7 Hz, 1H, H-1), 4.81 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.63 (t, *J* = 4.1 Hz, 1H, H-2), 4.58 (d, *J* = 11.3 Hz, 1H, CH*H* Bn), 4.13 (dd, *J* = 8.9, 3.4 Hz, 1H, H-4), 4.07 – 4.00 (m, 1H, H-5), 3.96 (dd, *J* = 8.9, 4.4 Hz, 1H, H-3), 3.77 – 3.64 (m, 2H, H-6), 1.62 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7 (C_q Bn), 128.6, 128.4, 128.3 (CH_{Ar} Bn), 113.2 (C_q isopropyl), 104.2 (C-1), 79.1 (C-4), 77.4 (C-2), 76.8 (C-3), 72.2 (CH_2 Bn), 70.1 (C-5), 63.1 (C-6), 26.8, 26.6 (2 x CH_3).

3,6-Di-*O*-Benzyl-1,2-di-*O*-isopropylidene-α-D-*allo*-furanose (42):



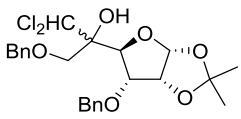
42 was synthesized from **41** (0.45 g, 1.45 mmol) in a yield of 76% (0.44 g, 1.10 mmol), as thick yellow oil, as described for the synthesis of **12**. R_F = 0.27 (10:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 10H, H_{Ar} Bn), 5.75 (d, *J* = 3.7 Hz, 1H, H-1), 4.74 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.57 – 4.54 (m, 3H, 2 x CH*H* Bn, H-2), 4.56 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.15 (m, 1H, H-5), 4.14 – 4.09 (m, 1H, H-4), 3.98 (dd, *J* = 8.7, 4.4 Hz, 1H, H-3), 3.60 – 3.55 (m, 2H, H_2-6), 1.61 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.5 (C_q Bn), 128.5 – 127.6 (CH_{Ar} Bn), 113.0 (C_q isopropyl), 104.2 (C-1), 78.5 (C-4), 77.7 (C-2), 77.1(C-3), 73.4, 72.1 (CH_2 Bn), 70.7 (C-6), 70.1 (C-5), 26.9, 26.7 (2 x CH_3).

1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-α-D-*ribo*-hexofurano-5-ulose (43):



43 was synthesized from **42** (14.0 g, 35.0 mmol) in a yield of 64% (8.91 g, 22.4 mmol), as described for the synthesis of **13**. R_F = 0.4 (10:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.21 (m, 10H, H_{Ar} Bn), 5.77 (d, *J* = 3.5 Hz, 1H, H-1), 4.72 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.63 – 4.55 (m, 4H, 2 x CH*H* Bn, H-6, H-4), 4.54 – 4.52 (m, 1H, H-2), 4.31 (d, *J* = 5.0 Hz, 2H, CH_2 Bn), 3.82 (dd, *J* = 9.0, 4.3 Hz, 1H, H-3), 1.58 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8 (C=O), 137.1, 136.9 (C_q Bn), 128.6 – 128.0 (CH_{Ar} Bn), 113.7 (C_q), 104.6 (C-1), 80.4 (C-4), 79.3 (C-3), 77.7 (C-2), 73.3 (CH_2 Bn), 72.8 (C-6), 72.4 (CH_2 Bn), 26.9, 26.6 (2 x CH_3).

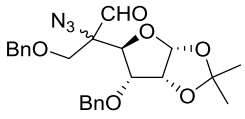
1,2-*O*-Isopropyl-3,6-di-*O*-benzyl-5-*C*-dichloroemethyl-α-D-*allo*/β-L-talo-furanoside (44):



44 was synthesized from **43** (10.0 g, 25.1 mmol) in a yield of 99% (12.0 g, 24.8 mmol) as two inseparable isomers (ratio 1:1) as described for the synthesis of **14**. R_F = 0.63 (5:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 10H, H_{Ar} Bn), 6.12 (s, 1H, C*H*Cl_2), 5.78 (d, *J* = 3.6 Hz, 1H, H-1), 4.70 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.58 – 4.52 (m, 3H, H_2-6, H-2), 4.49 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.41 (d, *J* = 8.3 Hz, 1H, H-4), 4.12 (dd, *J* = 8.3, 4.4 Hz, 1H, H-3), 3.90 (d, *J* = 10.2 Hz, 1H, CH*H* Bn), 3.74 (d, *J* = 10.2 Hz, 1H, CH*H* Bn), 1.60 (s, 3H, CH_3), 1.38 (s, 3H,

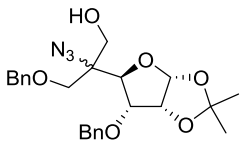
CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 137.3 (C_q Bn), 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8 (CH_{Ar} Bn), 113.5 (C_q isopropyl), 104.1 (C-1), 78.9 (C-4), 77.9 (C-2), 77.8 (C-3), 76.1 (C-5), 75.8 ($CHCl_2$), 73.8 (C-6), 72.1 (CH_2 Bn), 67.1 (CH_2 Bn), 27.1, 26.9 (2 x CH_3).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*allo*/β-L-*talo*-furano-1,6-dialdose (45):



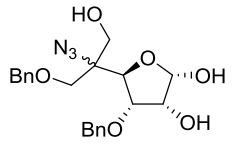
45 was synthesized from **44** (12.0 g, 24.8 mmol) in a yield of 71% (7.99 g, 17.6 mmol), as described for the synthesis of **15**. R_F = 0.25 (10:1, PE:EtOAc). **45** is an inseparable mixture of diastereomers (ratio = 5:3). NMR data of the major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H, CHO), 7.50 – 7.20 (m, 10H, H_{Ar} Bn), 5.73 (d, *J* = 3.5 Hz, 1H, H-1), 4.64 – 4.42 (m, 5H, 2 x CH*H* Bn, H_2-6, H-2), 4.35 (d, *J* = 8.7 Hz, 1H, H-4), 4.12 (d, *J* = 10.0 Hz, 1H, CH*H* Bn), 3.99 (d, *J* = 10.0 Hz, 1H, CH*H* Bn), 3.97 (dd, *J* = 8.7, 4.3 Hz, 1H, H-3), 1.59 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7 (CHO), 137.0, 136.7 (C_q Bn), 128.6 – 127.7 (CH_{Ar} Bn), 113.6 (C_q isopropyl), 104.6 (C-1), 77.8 C-4), 77.2 (C-3), 76.9 (C-2), 73.8 (C-6), 72.4, 71.0 (2 x CH_2 Bn), 69.5 (C-5), 26.9, 26.4 (2 x CH_3).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-1,2-*O*-isopropyl-α-D-*allo*/β-L-*talo*-furanoside (46):



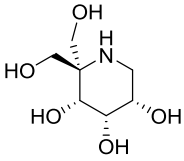
46 was synthesized from **45** (7.46 g, 16.5 mmol) in a yield of 81% (6.06 g, 13.3 mmol) as two inseparable diastereomers as described for the synthesis of **16**. R_F = 0.23 (9:1, PE:EtOAc). NMR-data of the major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 10H, H_{Ar} Bn), 5.82 (d, *J* = 3.7 Hz, 1H, H-1), 4.81 (d, *J* = 11.0 Hz, 1H, CH*H* Bn), 4.67 – 4.60 (m, 3H, H_2-6, H-2), 4.58 (d, *J* = 11.0 Hz, 1H, CH*H* Bn), 4.22 (d, *J* = 8.6 Hz, 1H, H-4), 4.11 – 4.08 (m, 1H, H-3), 3.93 (d, *J* = 9.9 Hz, 1H, CH*H* Bn), 3.86 (d, *J* = 9.9 Hz, 1H, CH*H* Bn), 3.86 (d, *J* = 9.9 Hz, 1H, CH*H*OH), 3.67 (dd, *J* = 9.9, 3.7 Hz, 1H, CH*H*OH), 1.60 (s, 3H, CH_3), 1.41 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.4 (C_q Bn), 128.7 – 127.7 (CH_{Ar} Bn), 113.4 (C_q isopropyl), 104.3 (C-1), 79.5 (C-4), 77.8 (C-3), 77.2 (C-2), 73.7 (C-6), 72.3, 69.9 (CH_2 Bn), 66.6 (C-5), 62.3 (CH_2OH), 26.9, 26.7 (2 x CH_3).

5-Deoxy-5-azido-5-*C*-benzyloxymethyl-3-*O*-benzyl-α-D-*allo*/β-L-*talo*-furanoside (47):



47 was synthesized from **46** (1.40 g, 3.07 mmol) in a yield of 70% (0.89 g, 2.15 mmol), as two inseparable diastereoisomer (ratio = 5:3) as described for the synthesis of **17**. R_F = 0.15 (5:3, PE:EtOAc). NMR data of the major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 10H, H_{Ar} Bn), 5.29 (s, 1H, H-1), 4.71 – 4.38 (m, 5H, CH_2 Bn, H_2-6, H-2), 4.30 – 4.23 (m, 1H, H-4), 4.08 – 4.03 (m, 1H, H-3), 3.81 – 3.73 (m, 2H, CH_2 Bn), 3.69 – 3.51 (m, 2H, C*H*$_2$OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 – 127.7 (CH_{Ar} Bn), 96.9 (C-1), 81.5 (C-4), 77.9 (C-2), 77.0 (C-3), 73.8 (C-6), 72.9 (CH_2 Bn), 69.5 (CH_2 Bn), 66.6 (C-5), 62.9 (CH_2OH).

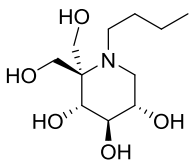
5-*C*-Hydroxymethyl-1-deoxy-D-allonojirimycin (9):



9 was synthesized from **47** (0.79 g, 1.90 mmol) in a yield of 81% (0.30 g, 1.54 mmol) as described for the synthesis of **6**. ^1H NMR (400 MHz, MeOD) δ 4.02 (d, *J* = 11.5 Hz, 1H, H-6a), 3.98 (t, *J* = 3.2 Hz, 1H, H-3), 3.81 (d, *J* = 3.2 Hz, 1H, H-4), 3.75 – 3.71 (m, 1H, H-2), 3.73 (d, *J* = 10.8Hz, 1H, H-6*a), 3.67 (d, *J* = 11.6 Hz, 1H, H-6b), 3.59 (d, *J* = 11.1 Hz, 1H, H-6*b), 3.03 (dd, *J* = 13.1, 8.2 Hz, 1H, H-1a), 2.87 (dd, *J* = 13.1, 4.0 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 70.0 (C-3), 69.5 (C-4), 68.3 (C-2), 61.3 (C-6), 60.8 (C-6*), 60.3 (C-5), 42.3 (C-1). $[\alpha]^{20}_D$ = +0.23 (c =1.31, MeOH). IR/cm^{-1}: 3263, 2900, 1607, 1450, 1413, 1257, 1033. HRMS: found 194.10218 $[M+H]^+$, calculated for $[C_7H_{15}NO_5+H]^+$ 194.10230.

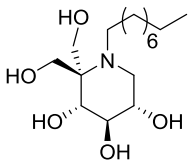
N-Alkylated final compounds:

5-*C*-Hydroxymethyl-*N*-butyl-1-deoxynojirimycin (56):



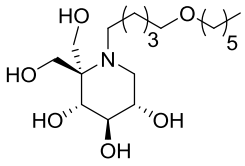
6 (0.10 mmol) and butyl bromide (0.16 mmol) was subjected to general alkylation procedure to provide **56** (0.5 mg, 0.002 mmol, yield 2%). ^{1}H NMR (600 MHz, MeOD) δ 4.04 (d, *J* = 13.3 Hz, 1H, H-6a), 3.90 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.87 (d, *J* = 12.9 Hz, 1H, H-6b), 3.86 (t, *J* = 9.6 Hz, 1H, H-3), 3.78 (d, *J* = 12.0 Hz, 1H, H-6*b), 3.76 – 3.72 (m, 1H, H-2), 3.68 (d, *J* = 10.0 Hz, 1H, H-4), 3.59 – 3.51 (m, 2H, H-1a, H-1'a), 3.47 – 3.43 (m, 1H, H-1b), 3.14 (td, *J* = 12.3, 5.0 Hz, 1H, H-1'b), 1.93 – 1.83 (m, 1H, H-2'a), 1.78 – 1.68 (m, 1H, H-2'b), 1.53 – 1.41 (m, 2H, H_2-3'), 1.04 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (150 MHz, MeOD) δ 74.1 (C-3), 72.9 (C-5), 70.0 (C-4), 67.9 (C-2), 56.8 (C-6*), 56.5 (C-6), 52.6 (C-1), 52.5 (C-1'), 27.9 (C-2'), 20.7 (C-3'), 13.5 (C-4'). IR/cm^{-1}: 3471, 2970, 1738, 1442, 1365, 1216, 1139. $[\alpha]^{20}_D$ = -2.00 (c = 0.01, MeOH). HRMS: found 250.16502 $[C_{11}H_{23}NO_5+H]^+$, calculated for $[C_{11}H_{23}NO_5+H]^+$ 250.16490.

5-*C*-Hydroxymethyl-*N*-nonyl-1-deoxynojirimycin (57):



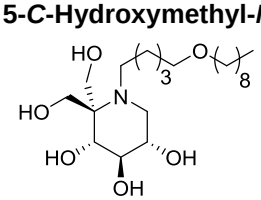
6 (0.20 mmol) and nonyl bromide (0.31 mmol) was subjected to general alkylation procedure to provide **57** (5.0 mg, 0.016 mmol, yield 8%). ^{1}H NMR (600 MHz, MeOD) δ 4.04 (d, *J* = 13.3 Hz, 1H, H-6a), 3.90 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.86 (d, *J* = 13.6 Hz, 1H, H-6b), 3.86 (t, *J* = 10.0 Hz, 1H, H-3), 3.77 (d, *J* = 11.9 Hz, 1H, H-6*b), 3.78 – 3.71 (m, 1H, H-2), 3.68 (d, *J* = 10.0 Hz, 1H, H-4), 3.58 – 3.50 (m, 2H, H-1a, H-1'a), 3.44 (t, *J* = 11.7 Hz, 1H, H-1b), 3.12 (td, *J* = 12.3, 5.0 Hz, 1H, H-1'b), 1.96 – 1.83 (m, 1H, H-2'a), 1.80 – 1.70 (m, 1H, H-2'b), 1.47 – 1.25 (m, 12H, H_2-3', H_2-4', H_2-5', H_2-6', H_2-7', H_2-8'), 0.93 (t, *J* = 7.1 Hz, 3H, H_3-9'). ^{13}C NMR (150 MHz, MeOD) δ 74.0 (C-3), 72.9 (C-5), 70.0 (C-4), 67.9 (C-2), 56.8 (C-6*), 56.5 (C-6), 52.6 (C-1'), 52.6 (C-1), 32.6 , 30.1, 29.9, 29.9, 27.4, 25.9, 23.3, 14.0 (C-2' – C-9'). IR/cm^{-1}: 3675, 2988, 2901, 1677, 1394, 1226, 1056. $[\alpha]^{20}_D$ = -0.1 (c = 0.10, MeOH). HRMS: found 320.24321 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

5-*C*-Hydroxymethyl-*N*-[5-(hexyloxy)pentyl]-1-deoxynojirimycin (58):



6 (0.20 mmol) and pentyloxyhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **58** (3.0 mg, 0.008 mmol, yield 4%). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (d, *J* = 13.3 Hz, 1H, H-6a), 3.88 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.84 (t, *J* = 9.6 Hz, 1H, H-3), 3.84 (d, *J* = 13.2 Hz, 1H, H-6b), 3.75 (d, *J* = 11.9 Hz, 1H, H-6*b), 3.75 – 3.69 (m, 1H, H-2), 3.66 (d, *J* = 10.0 Hz, 1H, H-4), 3.56 – 3.50 (m, 2H, H-1a, H-1'a), 3.44 – 3.40 (m, 1H, H-1b), 3.46 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.43 (t, *J* = 6.7 Hz, 2H, H_2-6'), 3.12 (td, *J* = 12.2, 5.0 Hz, 1H, H-1'b), 1.94 – 1.86 (m, 1H, H-2'a), 1.81 – 1.69 (m, 1H, H-2'b), 1.68 – 1.60 (m, 2H, H_2-4'), 1.60 – 1.53 (m, 2H, H_2-7'), 1.52 – 1.43 (m, 2H, H_2-3'), 1.40 – 1.26 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.91 (t, *J* = 6.9 Hz, 3H, H_3-11'). ^{13}C NMR (150 MHz, MeOD) δ 74.4 (C-3), 73.3 (C-5), 72.1 (C-6'), 71.4 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 52.9 (C-1'), 32.9 (C-9'), 30.7 (C-7'), 30.2 (C-4'), 27.0 (C-8'), 26.1 (C-2'), 24.6 (C-3'), 23.7 (C-10'), 14.4 (C-11'). IR/cm^{-1}: 3316, 2933, 1673, 1439, 1366, 1205, 1135. $[\alpha]^{20}_D$ = -1.00 (c = 0.06, MeOH). HRMS: found 364.26940 $[C_{18}H_{37}NO_6+H]^+$, calculated for $[C_{18}H_{37}NO_6+H]^+$ 364.26936.

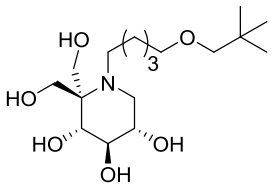
5-*C*-Hydroxymethyl-*N*-[5-(nonyloxy)pentyl]-1-deoxynojirimycin (59):



6 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **59** (2.4 mg, 0.006 mmol, yield 3%). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (d, *J* = 13.3 Hz, 1H, H-6a), 3.88 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.84 (t, *J* = 9.6 Hz, 1H, H-3), 3.84 (d, *J* = 13.8 Hz, 1H, H-6b), 3.74 (d, *J* = 12.0 Hz, 1H, H-6*b), 3.73 – 3.69

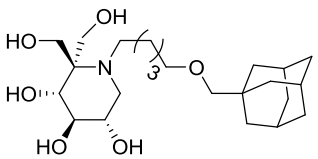
(m, 1H, H-2), 3.66 (d, *J* = 10.0 Hz, 1H, H-4), 3.57 – 3.49 (m, 2H, H-1a, H-1'a), 3.46 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.43 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.44 – 3.40 (m, 1H, H-1b), 3.12 (td, *J* = 12.2, 5.0 Hz, 1H, H-1'b), 1.90 (ddt, *J* = 20.9, 12.1, 5.8 Hz, 1H, H-2'a), 1.75 (dtt, *J* = 22.4, 12.0, 5.1 Hz, 1H, H-2'b), 1.68 – 1.61 (m, 2H, H_2-4'), 1.59 – 1.53 (m, 2H, H_2-7'), 1.53 – 1.42 (m, 2H, H_2-3'), 1.40 – 1.23 (m, 12H, H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.90 (t, *J* = 7.0 Hz, 3H, H_3-14'). ^{13}C NMR (150 MHz, MeOD) δ 74.4 (C-3), 73.3 (C-5), 72.1 (C-6'), 71.4(C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 52.9 (C-1'), 33.1 (C-9'), 30.8 (C-7'), 30.7, 30.6 30.4 (C-10', C-11', C-12'), 30.2 (C-4'), 27.3 (C-8'), 26.1 (C-2'), 24.6 (C-3'), 23.7 (C-13'), 14.4 (C-14'). $[\alpha]^{20}_D$ = -0.63 (c = 0.05, MeOH). IR/cm^{-1}: 3357, 2928, 1738, 1676, 1438, 1365, 1216, 1137, 801, 724, 527. HRMS: found 406.31624 $[C_{21}H_{43}NO_6+H]^+$, calculated for $[C_{21}H_{43}NO_6+H]^+$ 406.31631.

5-*C*-Hydroxymethyl-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxynojirimycin (60):



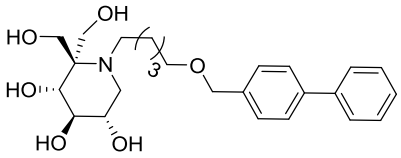
6 (0.10 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy) pentane (0.15 mmol) was subjected to general alkylation procedure to provide **60** (1.1 mg, 0.0032 mmol, yield 3%). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (d, *J* = 13.3 Hz, 1H, H-6a), 3.88 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.84 (d, *J* = 13.3 Hz, 1H, H-6b), 3.75 (d, *J* = 12.0 Hz, 1H, H-6*b), 3.86 – 3.81 (m, 1H, H-3), 3.75 – 3.69 (m, 1H, H-2), 3.65 (d, *J* = 10.0 Hz, 1H, H-4), 3.56 – 3.50 (m, 2H, H-1a, H-1'a), 3.45 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.44 – 3.38 (m, 1H, H-1b), 3.12 (td, *J* = 12.2, 5.0 Hz, 1H, H-1'b), 3.08 (s, 2H, H_2-6'),1.94 – 1.89 (m, 1H, H-2'a), 1.77 – 1.73 (m, 1H, H-2'b), 1.69 – 1.65 (m, 2H, H_2-3'), 1.61 – 1.42 (m, 2H, H_2-4'), 0.91 (s, 9H, 3 x CH_3). ^{13}C NMR (150 MHz, MeOD) δ 82.6 (C-6'), 74.4 (C-3), 73.3 (C-5), 72.0 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1), 53.0 (C-1'), 32.9 (C_q), 30.3 (C-4'), 27.1 (C-2'), 26.2 (C-3'), 24.6 (3 x CH_3). $[\alpha]^{20}_D$ = -1.36 (c = 0.02, MeOH). IR/cm^{-1}: 3460, 3016, 2970, 1738, 1442, 1365, 1216, 1132. HRMS: found 350.25376 $[C_{17}H_{35}NO_6+H]^+$, calculated for $[C_{17}H_{35}NO_6+H]^+$ 350.25371.

5-*C*-Hydroxymethyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (61):



6 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.29 mmol) was subjected to general alkylation procedure to provide **61** (9.1 mg, 0.022 mmol, yield 11%). ^{1}H NMR (600 MHz, MeOD) δ 4.02 (d, *J* = 13.4 Hz, 1H, H-6a), 3.88 (d, *J* = 12.2 Hz, 1H, H-6b), 3.85 (d, *J* = 13.8 Hz, H-6*a), 3.86 – 3.82 (m, 1H, H-3), 3.76 (d, *J* = 12.2 Hz, 1H, H-6*b), 3.76 – 3.72 (m, 1H, H-2), 3.66 (d, *J* = 10.0 Hz, 1H, H-4), 3.55 – 3.50 (m, 2H, H-1a, H-1'a), 3.42 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.43 – 3.39 (m, 1H, H- 1b) 3.16 – 3.08 (m, 1H, H-1'b), 2.99 (s, 2H, H_2-6'), 1.94 (p, *J* = 3.0 Hz, 3H, 3 x CH ada), 1.94 – 1.90 (m, 1H, H-2'a), 1.77 – 1.66 (m, 7H, 3 x CH_2 ada, H-2'b), 1.63 (m, 2H, H_2-4'), 1.56 (d, *J* = 2.9 Hz, 6H, 3 x CH_2 ada), 1.53 – 1.41 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 83.1 (C-6'), 74.4 (C-3), 73.2 (C-5), 72.1 (C-5'), 70.4 (C-4), 68.2 (C-2), 57.2 (C-6), 56.9 (C-6*), 53.0 (C-1'), 52.9 (C-1), 40.8 (CH_2 ada), 38.3 (CH_2 ada), 35.1 (C_q ada), 30.1 (C-4'), 29.7 (CH ada), 26.1 (C-2'), 24.6 (C-3'). $[\alpha]^{20}_D$ = -0.77 (c = 0.18, MeOH). IR/cm^{-1}: 3346, 2902, 2848, 1738, 1673, 1448, 1365, 1205, 1136. HRMS: found 428.30048 $[C_{23}H_{41}NO_6+H]^+$, calculated for $[C_{23}H_{41}NO_6+H]^+$ 428.30066.

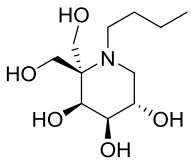
5-*C*-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxynojirimycin (62):



6 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **62** (40.8 mg, 0.092 mmol, yield 46%). ^{1}H NMR (600 MHz, MeOD) δ 7.63 (dd, *J* = 8.3, 1.7 Hz, 4H, H_{Ar} BiPh), 7.48 – 7.41 (m, 4H, H_{Ar} BiPh), 7.39 – 7.32 (m, 1H, H_{Ar} BiPh), 4.58 (s, 2H, H_2-6'), 4.03 (d, *J* = 13.3 Hz, 1H, H-6a), 3.90 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.86 (d, *J* = 10.1 Hz, 1H, H-3), 3.86 (d, *J* = 13.2 Hz, 1H, H-6b), 3.77 (d, *J* = 12 Hz, 1H, H-6*b), 3.77 – 3.63 (m, 1H, H-2), 3.68 (d, *J* = 10.0 Hz, 1H, H-4), 3.59

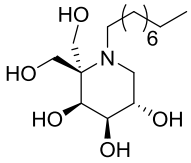
(t, *J* = 6.2 Hz, 2H, H_2-5'), 3.57 – 3.51 (m, 2H, H-1a, H-1'a), 3.44 (t, *J* = 11.8 Hz, 1H, H-1b), 3.15 (td, *J* = 12.2, 5.0 Hz, 1H, H-1'b), 2.01 – 1.86 (m, 1H, H-2'a), 1.84 – 1.76 (m, 1H, H-2'b), 1.76 – 1.69 (m, 2H, H_2-4'), 1.64 – 1.45 (m, 2H, H_2-3'a). ^{13}C NMR (150 MHz, MeOD) δ 141.7, 141.5 (C_q BiPh), 138.5 – 127.5 (C_{Ar} BiPh), 74.1 (C-3), 73.3 (C-6'), 72.9 (C-5), 70.6 (C-5'), 70.1 (C-4), 67.9 (C-2), 56.8 (C-6), 56.5 (C-6*), 52.6 (C-1), 52.6 (C-2), 29.8 (C-4'), 25.7 (C-2'), 24.3 (C-3'). $[\alpha]^{20}_D$ = -0.1 (c = 0.82, MeOH). IR/cm^{-1}: 3361, 3016, 2970, 1738, 1675, 1440, 1365, 1205, 1134. HRMS: found 446.25357 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

5-*C*-Hydroxymethyl-*N*-butyl-1-deoxy-D-galactonojirimycin (77):



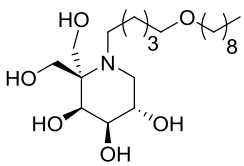
7 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **77** (11.2 mg, 0.044 mmol, yield 22%). ^{1}H NMR (600 MHz, MeOD) δ 4.27 (d, *J* = 3.4 Hz, 1H, H-4), 4.24 (d, *J* = 14.0 Hz, 1H, H-6a), 4.00 (td, *J* = 4.8, 1.8 Hz, 1H, H-2), 3.98 (d, *J* = 11.4 Hz, 1H, H-6*a), 3.94 (t, *J* = 4.1 Hz, 1H, H-3), 3.89 (d, *J* = 12 Hz, 1H, H-6*b), 3.89 (d, *J* = 14.4 Hz, 1H, H-6b), 3.76 (dd, *J* = 13.1, 1.6 Hz, 1H, H-1a), 3.62 (ddd, *J* = 13.1, 10.1, 6.6 Hz, 1H, 1'a), 3.42 (dd, *J* = 13.8, 3.6 Hz, 1H, H-1b), 3.24 – 3.17 (m, 1H, H-1'b), 1.89 – 1.79 (m, 1H, H-2'a), 1.74 – 1.64 (m, 1H, H-2'b), 1.52 – 1.36 (m, 2H, H_2-3'), 1.01 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (150 MHz, MeOD) δ 73.6 (C-5), 70.2 (C-3), 66.8 (C-2), 65.1 (C-4), 56.9 (C-6*), 56.5 (C-6), 51.8 (C-1'), 49.5 (C-1), 28.5 (C-2'), 20.0 (C-3'), 13.5 (C-4'). $[\alpha]^{20}_D$ = +0.04 (c = 0.22, MeOH). IR/cm^{-1}: 3271, 2968, 2879, 1674, 1435, 1201, 1134, 1082. HRMS: found 250.16488 $[C_{11}H_{23}NO_5+H]^+$, calculated for $[C_{11}H_{23}NO_5+H]^+$ 250.16490.

5-*C*-Hydroxymethyl-*N*-nonyl-1-deoxy-D-galactonojirimycin (78):



7 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **78** (11.8 mg, 0.036 mmol, yield 18%). ^{1}H NMR (400 MHz, MeOD) δ 4.30 (d, *J* = 3.3 Hz, 1H, H-4), 4.27 (d, *J* = 14.0 Hz, 1H, H-6a), 4.04 – 4.00 (m, 1H, H-2), 4.00 (d, *J* = 11.9 Hz, 1H, H-6*a), 3.98 – 3.95 (m, 1H, H-3), 3.91 (d, *J* = 11.5 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.2 Hz, 1H, H-6b), 3.78 (dd, *J* = 13.0, 1.6 Hz, 1H, H-1a), 3.63 (ddd, *J* = 13.0, 10.0, 6.7 Hz, 1H, H-1'a), 3.43 (dd, *J* = 13.1, 3.4 Hz, 1H, H-1b), 3.23 (ddd, *J* = 13.6, 9.6, 4.9 Hz, 1H, H-1'b), 1.96 – 1.82 (m, 1H, H-2'a), 1.80 – 1.66 (m, 1H, H-2'b), 1.51 – 1.28 (m, 12H, H_2-3', H_2-4', H_2-5', H_2-6', H_2-7', H_2-8'), 0.93 (t, *J* = 7.1 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 72.6 (C-5), 69.2 (C-3), 65.8 (C-2), 64.1 (C-4), 55.8 (C-6*), 55.4 (C-6), 51.0 (C-1'), 48.4 (C-1), 31.6, 29.1, 28.9, 28.8, 25.7, 25.4, 22.3 (C-2' – C-8'), 13.0 (C-9'). $[\alpha]^{20}_D$ = +0.0 (c = 0.24, MeOH). IR/cm^{-1}: 3336, 2928, 1738, 1673, 1438, 1365, 1204, 1136, 1080. HRMS: found 320.24316 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

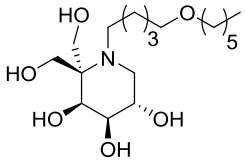
5-*C*-Hydroxymethyl-*N*-[5-(hexyloxy)pentyl]-1-deoxy-D-galactonojirimycin (79):



7 (0.20 mmol) and pentyloxyhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **79** (15.3 mg, 0.042 mmol, yield 21%). ^{1}H NMR (400 MHz, MeOD) δ 4.30 (d, *J* = 3.3 Hz, 1H, H-4), 4.26 (d, *J* = 14.0 Hz, 1H, H-6a), 4.05 – 4.02 (m, 1H, H-2), 4.00 (d, *J* = 12.0 Hz, 1H, H-6*a), 3.98 – 3.95 (m, 1H, H-3), 3.92 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.1 Hz, 1H, H-6b), 3.79 (dd, *J* = 13.1, 1.3 Hz, 1H, H-1a), 3.64 (ddd, *J* = 13.2, 10.1, 6.6 Hz, 1H, H-1'a), 3.48 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.45 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.43 (dd, *J* = 13.2, 3.5 Hz, 1H, H-1b), 3.24 (ddd, *J* = 13.0, 9.7, 4.4 Hz, 1H, H-1'b), 1.99 – 1.85 (m, 1H, H-2'a), 1.85 – 1.71 (m, 1H, H-2'b), 1.71 – 1.62 (m, 2H, H_2-4'), 1.57 (dt, *J* = 7.9, 6.6 Hz, 2H, H_2-7'), 1.54 – 1.43 (m, 2H, H_2-3'), 1.42 – 1.28 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 7.1 Hz, 3H, H_3-11'). ^{13}C NMR (150 MHz, MeOD) δ 71.8 (C-6'), 71.1 (C-5'), 70.5 (C-3), 66.8 (C-2), 65.3 (C-4), 58.4 (C-6*), 57.1(C-6), 52.2 (C-1'), 49.8 (C-1), 32.6 (C-10'), 30.5 (C-7'), 29.9 (C-4'), 26.7 (C-8'), 26.3 (C-2'), 23.9 (C-3'), 23.5 (C-9'), 14.2 (C-10'). $[\alpha]^{20}_D$ = +0.1 (c = 0.31, MeOH). IR/cm^{-1}: 3346, 2931,

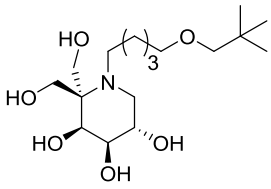
2860, 1670, 1458, 1431, 1201, 1132, 1082. HRMS: found 364.26934 $[C_{18}H_{37}NO_6+H]^+$, calculated for $[C_{18}H_{37}NO_6+H]^+$ 364.26936.

5-*C*-Hydroxymethyl-*N*-[5-(nonyloxy)pentyl]-1-deoxy-D-galactonojirimycin (80):



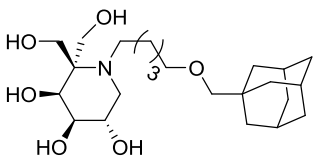
7 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **80** (11.5 mg, 0.028 mmol, yield 14%). ^{1}H NMR (400 MHz, MeOD) δ 4.29 (d, *J* = 3.3 Hz, 1H, H-4), 4.26 (d, *J* = 14.0 Hz, 1H, H-6a), 4.03 – 4.01 (m, 1H, H-2), 4.00 (d, *J* = 11.8 Hz, 1H, H-6*a), 3.97 – 3.94 (m, 1H, H-3), 3.91 (d, *J* = 11.2 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.2 Hz, 1H, H-6b), 3.79 (dd, *J* = 13.1, 1.6 Hz, 1H, H-1a), 3.69 – 3.56 (m, 1H, H-1'a), 3.47 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.44 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.45 – 3.42 (m, 1H, H-1b), 3.23 (ddd, *J* = 14.1, 9.8, 4.4 Hz, 1H, H-1'b), 1.99 – 1.85 (m, 1H, H-2'a), 1.80 – 1.72 (m, 1H, H-2'b), 1.65 (dt, *J* = 8.1, 6.1 Hz, 2H, H_2-4'), 1.60 – 1.53 (m, 2H, H_2-7'), 1.53 – 1.41 (m, 2H, H_2-3'), 1.39 – 1.26 (m, 12H, H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.93 (t, *J* = 6.8 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 72.6 (C-5), 70.7 (C-6'), 69.9 (C-5'), 69.2 (C-3), 65.8 (C-2), 64.2 (C-4), 55.9 (C-6*), 55.5 (C-6), 50.9 (C-1'), 48.6 (C-1), 31.6 (C-9'), 29.4 (C-7'), 29.3, 29.2, 29.0 (C-10', C-11', C-12'), 28.7 (C-4'), 25.9 (C-8'), 25.2 (C-2'), 22.6 (C-3'), 22.3 (C-13'), 13.0 (C-14'). IR/cm^{-1}: 3675, 3353, 2971, 2924, 1674, 1394, 1203, 1067. $[\alpha]^{20}_D$ = +0.1 (c = 0.23, MeOH). HRMS: found 406.31615 $[C_{21}H_{43}NO_6+H]^+$, calculated for $[C_{21}H_{43}NO_6+H]^+$ 406.31631.

5-*C*-Hydroxymethyl-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-galactonojirimycin (81):



7 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy) pentane (0.30 mmol) was subjected to general alkylation procedure to provide **81** (14.3 mg, 0.04 mmol, yield 20%). ^{1}H NMR (400 MHz, MeOD) δ 4.30 (d, *J* = 3.3 Hz, 1H, H-4), 4.27 (d, *J* = 14.1 Hz, 1H, H-6a), 4.02 (td, *J* = 3.6, 1.6 Hz, 1H, H-2), 4.00 (d, *J* = 11.6 Hz, 1H, H-6*a), 3.97 (t, *J* = 3.6 Hz, 1H, H-3), 3.92 (d, *J* = 11.2 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.0 Hz, 1H, H-6b), 3.79 (dd, *J* = 13.1, 1.7 Hz, 1H, H-1a), 3.64 (ddd, *J* = 13.1, 10.1, 6.7 Hz, 1H, H-1'a), 3.47 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.44 (dd, *J* = 13.2, 3.2 Hz, 1H, H-1b), 3.28 – 3.20 (m, 1H, H-1'b), 3.10 (s, 2H, H_2-6'), 2.03 – 1.88 (m, 1H, H-2'a), 1.85 – 1.74 (m, 1H, H-2'b), 1.71 – 1.63 (m, 2H, H_2-4'), 1.61 – 1.42 (m, 2H, H_2-3'), 0.93 (s, 9H, 3 x CH_3). ^{13}C NMR (100 MHz, MeOD) δ 81.1 (C-6'), 72.6 (C-5), 70.6 (C-5'), 69.2 (C-3), 65.8 (C-2), 64.1 (C-4), 55.9 (C-6*), 55.5 (C-6), 50.9 (C-1'), 48.5 (C-1), 31.5 (C-7'), 28.8 (C-4'), 25.7 (CH_3), 25.3 (C-2'), 22.7 (C-3'). $[\alpha]^{20}_D$ = -0.1, (c = 0.29, MeOH). IR/cm^{-1}: 3675, 3327, 2971, 1673, 1393, 1202, 1066. HRMS: found 350.25364 $[C_{17}H_{35}NO_6+H]^+$, calculated for $[C_{17}H_{35}NO_6+H]^+$ 350.25371.

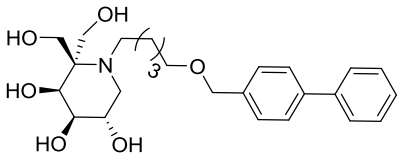
5-*C*-Hydroxymethyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-galactonojirimycin (82):



7 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **82** (36.5 mg, 0.09 mmol, yield 43%). ^{1}H NMR (400 MHz, MeOD) δ 4.28 (d, *J* = 3.0 Hz, 1H, H-4), 4.25 (d, *J* = 13.5 Hz, 1H, H-6a), 4.02 – 3.98 (m, 1H, H-2), 3.99 (d, *J* = 12.5 Hz, 1H, H-6*a), 3.95 (t, *J* = 3.9 Hz, 1H, H-3), 3.90 (d, *J* = 11.8 Hz, 1H, H-6*b), 3.90 (d, *J* = 13.7 Hz, 1H, H-6b), 3.77 (d, *J* = 12.9 Hz, 1H, H-1a), 3.62 (dt, *J* = 17.4, 8.1 Hz, 1H, H-1'a), 3.53 – 3.44 (m, 1H, H-1b), 3.42 (t, *J* = 6.1 Hz, 1H, H-5'), 3.28 – 3.16 (m, 1H, H-1'b), 2.98 (s, 2H, H_2-6'), 1.95 (t, *J* = 3.0 Hz, 3H, 3 x CH ada), 1.90 – 1.80 (m, 1H, H-2'a), 1.82 – 1.65 (m, 6H, 3 x CH_2 ada), 1.72 – 1.61 (m, 1H, H-2'b), 1.68 – 1.61 (m, 2H, H_2-4'), 1.57 (d, *J* = 2.8 Hz, 6H, 3 x CH_2 ada), 1.55 – 1.39 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (C-6'), 72.6 (C-5), 70.7 (C-5'), 69.2 (C-3), 65.4 (C-2), 64.1 (C-4), 55.8 (C-6*), 55.4 (C-6), 50.9 (C-1'), 47.7 (C-1), 39.4 (CH_2 ada), 36.9 (CH_2 ada), 33.7 (C_q ada), 28.7 (C-4'), 28.3 (CH ada), 25.3 (C-2'), 22.7 (C-3'). $[\alpha]^{20}_D$ = +0.2 (c = 0.73,

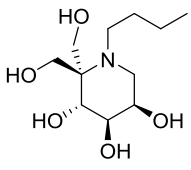
MeOH). IR/cm^{-1}: 3248, 2902, 2848, 1674, 1447, 1361, 1319, 1199, 1139, 1084, 1011. HRMS: found 428.30025 $[C_{23}H_{41}NO_6+H]^+$, calculated for $[C_{23}H_{41}NO_6+H]^+$ 428.30066.

5-*C*-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-galactonojirimycin (83):



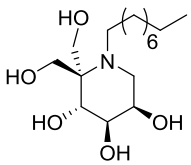
7 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **83** (18.6 mg, 0.04 mmol, yield 20%). ^{1}H NMR (400 MHz, MeOD) δ 7.68 – 7.60 (m, 4H, H_{Ar} BiPh), 7.52 – 7.41 (m, 4H, H_{Ar} BiPh), 7.39 – 7.32 (m, 1H, H_{Ar} BiPh), 4.57 (s, 2H, H_2-6'), 4.31 (d, *J* = 3.3 Hz, 1H, H-4), 4.26 (d, *J* = 14.0 Hz, 1H, H-6a), 4.02 – 3.99 (m, 1H, H-2), 4.00 (d, *J* = 11.7 Hz, 1H, H-6*a), 3.98 – 3.95 (m, 1H, H-3), 3.92 (d, *J* = 11.9 Hz, 1H, H-6*b), 3.91 (d, *J* = 14.1 Hz, 1H, H-6b), 3.76 (d, *J* = 13.0 Hz, 1H, H-1a), 3.69 – 3.61 (m, 1H, H-1'a), 3.58 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.41 (dd, *J* = 13.0, 3.4 Hz, 1H, H-1b), 3.28 – 3.20 (m, 1H, H-1'b), 1.99 – 1.84 (m, 1H, H-2'a), 1.83 – 1.75 (m, 1H, H-2'b), 1.73 (dt, *J* = 7.9, 6.1 Hz, 2H, H_2-4'), 1.65 – 1.43 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 132.0 – 128.6 (C_{Ar} BiPh), 74.9 (C-5), 74.5 (C-6'), 71.7 (C-5'), 71.4 (C-3), 68.0 (C-2), 66.4 (C-4), 58.1 (C-6*), 57.7 (C-6), 53.1 (C-1'), 50.8 (C-1), 30.9 (C-4'), 27.4 (C-2'), 24.9 (C-3'). $[\alpha]^{20}_D$ = +0.8 (c = 0.37, MeOH). IR/cm^{-1}: 3675, 3313, 2971, 1671, 1407, 1278, 1200, 1077, 1132. HRMS: found 446.25342 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

5-*C*-Hydroxymethyl-*N*-butyl-1-deoxy-D-mannonojirimycin (98):



8 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **98** (12.6 mg, 0.05 mmol, yield 25%). ^{1}H NMR (400 MHz, MeOD) δ 4.16 (td, *J* = 3.6, 1.2 Hz, 1H, H-2), 4.15 (d, *J* = 10 Hz, 1H, H-4) 4.06 (d, *J* = 13.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.6, 3.0 Hz, 1H, H-3), 3.92 (dd, *J* = 12.8, 0.8 Hz, 1H, H-1a), 3.90 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 12 Hz, 1H, H-6*a), 3.73 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.61 (dd, *J* = 12.8, 3.6 Hz, 1H, H-1b), 3.60 – 3.53 (m, 1H, H-1'a), 3.23 (ddd, *J* = 13.3, 9.7, 4.6 Hz, 1H, H-1'b), 1.96 – 1.82 (m, 1H, H-2'a), 1.74 (m, 1H, H-2'b), 1.52 – 1.44 (m, 2H, H_2-3'), 1.05 (t, *J* = 7.3 Hz, 3H, H_3-4'). ^{13}C NMR (100 MHz, MeOD) δ 74.7 (C-5), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4 (C-6*), 58.1 (C-6), 55.1 (C-1), 52.6 (C-1'), 29.6 (C-2'), 21.3 (C-3'), 14.8 (C-4'). $[\alpha]^{20}_D$ = -19.8 (c = 0.25, MeOH). IR/cm^{-1}: 3675, 3325, 2970, 1393, 1250, 1057. HRMS: found 250.16490 $[C_{11}H_{23}NO_5+H]^+$, calculated for $[C_{11}H_{23}NO_5+H]^+$ 250.16490

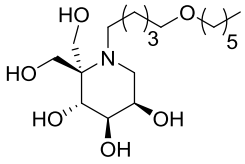
5-*C*-Hydroxymethyl-*N*-nonyl-1-deoxy-D-mannonojirimycin (99):



8 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **99** (16.3 mg, 0.052 mmol, yield 26%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 9.6 Hz, 1H, H-4), 4.13 (d, *J* = 3.6 Hz, 1H, H-2), 4.05 (d, *J* = 13.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.6, 3.2 Hz, 1H, H-3), 3.90 (d, *J* = 13.2 Hz, 1H, H-1a), 3.88 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 12 Hz, 1H, H-6*a), 3.72 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.59 (dd, *J* = 13.2, 3.6 Hz, 1H, H-1b), 3.58 – 3.52 (m, 1H, H-1'a), 3.27 – 3.16 (m, 1H, 1'b), 1.95 – 1.84 (m, 1H, H-2'a), 1.80 – 1.70 (m, 1H, H-2'b), 1.53 – 1.23 (m, 12H, H_2-3' – H_2-8'), 0.90 (t, *J* = 7.0 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 72.4 (C-5), 69.7 (C-3), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6), 55.8 (C-6*), 52.8 (C-1), 50.5 (C-1'), 31.6, 29.1, 28.9, 28.8, 25.7, 25.3, 22.3 (C-2' – C-8'), 13.0 (C-9'). $[\alpha]^{20}_D$ = -15.9 (c = 0.33, MeOH). IR/cm^{-1}: 3352, 2928, 2859, 1670, 1435, 1200, 1134, 1038. HRMS: found 320.24306 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

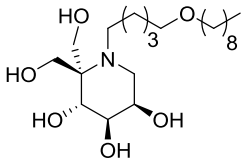
5-*C*-Hydroxymethyl-*N*-hexylpentyl-1-deoxy-D-mannonojirimycin (100):

8 (0.20 mmol) and pentyloxyhexyl bromide (0.31 mmol) was subjected to general alkylation procedure to provide **100** (14.0 mg, 0.038 mmol, yield 19%). ^{1}H NMR (400 MHz, MeOD) δ 4.14



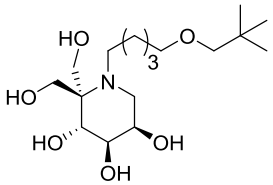
(d, *J* = 9,6 Hz, 1H, H-4), 4.14 (d, *J* = 4.0 Hz, 1H, H-2), 4.05 (d, *J* = 13.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.6, 3.0 Hz, 1H, H-3), 3.91 (d, *J* = 12 Hz, 1H, H-1a), 3.89 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 12 Hz, 1H, H-6*a), 3.72 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.60 (dd, *J* = 12.8, 3.2 Hz, 1H, H-1b), 3.60 – 3.51 (m, 1H, H-1'a), 3.48 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.45 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.26 – 3.19 (m, 1H, H-1'b), 2.01 – 1.72 (m, 2H, H_2-2'), 1.72 – 1.63 (m, 2H, H_2-4'), 1.63 – 1.53 (m, 2H, H_2-7'), 1.56 – 1.44 (m, 2H, H_2-3'), 1.43 – 1.29 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 6.7 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 72.4 (C-5), 70.7 (C-6'), 69.9 (C-5'), 69.7 (C-3), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6*), 55.8 (C-6), 52.9 (C-1), 50.4 (C-1'), 31.5 (C-9'), 29.4 (C-7'), 28.7 (C-4'), 25.6 (C-8'), 25.1 (C-2'), 22.6 (C-3'), 22.3 (C-10'), 13.0 (C-11'). $[\alpha]^{20}_D$ = -15.0 (c = 0.28, MeOH). IR/cm^{-1}: 3327, 2930, 2860, 1672, 1464, 1431, 1377, 1202, 1134, 1040. HRMS: found 364.27001 $[C_{18}H_{37}NO_6+H]^+$, calculated for $[C_{18}H_{37}NO_6+H]^+$ 364.26936.

5-*C*-Hydroxymethyl-*N*-nonylpentyl-1-deoxy-D-mannonojirimycin (101):



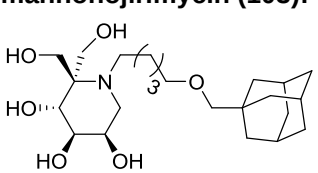
8 (0.20 mmol) pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **101** (14.2 mg, 0.034 mmol, yield 17%). ^{1}H NMR (400 MHz, MeOD) δ 3.98 (d, *J* = 9.9 Hz, 1H, H-4), 3.97 (d, *J* = 4.0 Hz, 1H, H-2), 3.93 – 3.87 (m, 1H, H-3), 3.91 (d, *J* = 12.5 Hz, 1H, H-6a), 3.86 (d, *J* = 12.4 Hz, 1H, H-6b), 3.84 (d, *J* = 11.4 Hz, 1H, H-6*a), 3.72 (d, *J* = 11.3 Hz, 1H, H-6*b), 3.47 (t, *J* = 6.6 Hz, 2H, H_2-5'), 3.45 (t, *J* = 6.7 Hz, 2H, H_2-6'), 3.53 – 3.42 (m, 1H, H-1a), 3.28 – 3.12 (m, 2H, H-1b, H-1'a), 2.82 – 2.58 (m, 1H, H-1'b), 1.78 – 1.53 (m, 6H, H_2-2', H_2-4', H_2-7'), 1.51 – 1.20 (m, 14H, H_2-3', H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.91 (t, *J* = 6.9 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 72.9 (C-6'),72.8 (C-5), 72.5 (C-5'), 70.8 (C-3), 68.9 (C-2), 67.5 (C-4), 53.7 (C-1), 51.6 (C-1'), 33.9 (C-9'), 31.7, 31.6, 31.6, 31.5, 31.4, 31.3, 28.1, 25.5, 24.6 (C-2', C-3', C-4', C-7', C-8', C-10', C-11', C-12', C-13'), 15.3 (C-14'). $[\alpha]^{20}_D$ = -15.5 (c = 0.28, MeOH). IR/cm^{-1}: 3357, 2928, 1738, 1676, 1438, 1365, 1216, 1137. HRMS: found 406.31603 $[C_{21}H_{43}NO_6+H]^+$, calculated for $[C_{21}H_{43}NO_6+H]^+$ 406.31631.

5-*C*-Hydroxymethyl-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-mannonojirimycin (102):



8 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy)pentane (0.30 mmol) was subjected to general alkylation procedure to provide **102** (11.7 mg, 0.034 mmol, yield 17%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 9.6 Hz, 1H, H-4), 4.14 (dd, *J* = 3.1, 1.1 Hz, 1H, H-2), 4.05 (d, *J* = 13.6 Hz, 1H, H-6a), 4.04 (dd, *J* = 9.9, 3.1 Hz, 1H, H-3), 3.92 (d, *J* = 12.8 Hz, 1H, H-1b), 3.89 (d, *J* = 13.2 Hz, 1H, H-6b), 3.87 (d, *J* = 11.2 Hz, 1H, H-6*a), 3.72 (d, *J* = 11.7 Hz, 1H, H-6*b), 3.61 (dd, *J* = 12.6, 3.5 Hz, 1H, H-1a), 3.58 – 3.53 (m, 2H, H_2-1'a), 3.48 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.29 – 3.19 (m, 1H, H-1'b), 3.11 (s, 2H, H_2-6'), 1.94 (m, 1H, H-2'a), 1.87 – 1.73 (m, 1H, H-2'b), 1.73 – 1.64 (m, 2H, H_2-3'), 1.54 (m , 2H, H_2-4'), 0.94 (s, 9H, 3 x CH_3). ^{13}C NMR (100 MHz, MeOD) δ 83.4 (C-6'), 73.5 (C-5),)72.9 (C-5'), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4, 58.1 (C-6, C-6*), 55.1 (C-1), 52.7 (C-1'), 33.8 (C-7') 31.1 (C-3'), 28.0 (3 x CH_3), 27.4 (C-2'), 25.0 (C-4'). $[\alpha]^{20}_D$ = -15.4 (c = 0.23, MeOH). IR/cm^{-1}: 3675, 2988, 2901, 1674, 1393, 1250, 1066. HRMS: found 350.25352 $[C_{17}H_{35}NO_6+H]^+$, calculated for $[C_{17}H_{35}NO_6+H]^+$ 350.25371.

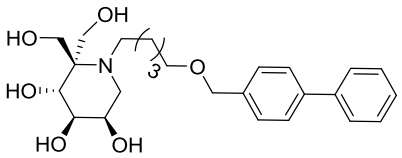
5-*C*-Hydroxymethyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-mannonojirimycin (103):



8 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **103** (10.5 mg, 0.024 mmol, yield 12%). ^{1}H NMR (400 MHz, MeOD) δ 4.14 (d, *J* = 9.6, 1H, H-4), 4.15 – 4.14 (m, 1H, H-2), 4.06 (d, *J* = 13.2, 1H, H-6a), 4.04 (dd, *J* = 9.6, 2.8, 1H, H-3), 3.92

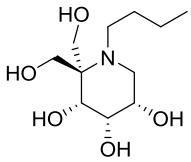
(dd, *J* = 13.2, 1.2, 1H, H-1b), 3.89 (d, *J* = 13.6, 1H, H-6b), 3.88 (d, *J* = 11.6, 1H, H-6*a), 3.73 (d, *J* = 11.7, 1H, H-6*b), 3.61 (dd, *J* = 12.9, 3.4 Hz, 1H, H-1a), 3.62 – 3.52 (m, 1H, H-1'a), 3.45 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.23 (ddd, *J* = 13.4, 9.9, 4.6 Hz, 1H, H-1'b), 1.98 (br s, 3H, CH ada), 1.96 – 1.89 (m, 1H, H-2'a), 1.85 – 1.75 (m, 1H, H-2'b), 1.83 – 1.68 (m, 6H, 3 x CH_2 ada), 1.70 – 1.63 (m, 2H, H_2-4'), 1.59 (d, *J* = 2.8 Hz, 6H, 3 x CH_2 ada), 1.57 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 84.0 (C-6'), 74.7 (C-5), 73.0 (C-5'), 72.0 (C-3), 69.4 (C-4), 67.9 (C-2), 58.4 (C-6*), 58.1 (C-6), 53.8 (C-1), 52.7 (C-1'), 41.7 (CH_2 ada), 39.2 (CH_2 ada), 36.0 (C_q ada), 31.0 (C-4'), 30.6 (CH ada), 27.5 (C-2'), 25.0 (C-3'). $[\alpha]^{20}_D$ = -13.3 (c = 0.21, MeOH). IR/cm^{-1}: 3675, 3330, 2901, 1673, 1450, 1203, 1134, 1077. HRMS: found 428.2999 $[C_{23}H_{41}NO_6+H]^+$, calculated for $[C_{23}H_{41}NO_6+H]^+$ 428.30066.

5-*C*-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-mannonojirimycin (104):



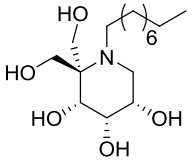
8 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.32 mmol) was subjected to general alkylation procedure to provide **104** (17.1 mg, 0.038 mmol, yield 19%). ^{1}H NMR (400 MHz, MeOD) δ 7.64 (m, 4H, H_{Ar} BiPh), 7.50 – 7.40 (m, 4H, H_{Ar} BiPh), 7.40 – 7.29 (m, 1H, H_{Ar} BiPh), 4.58 (s, 2H, H_2-6'), 4.14 (d, *J* = 9.8 Hz, 1H, H-4), 4.15 - 4.11 (t, *J* = 3.2 Hz, 1H, H-2), 4.04 (d, *J* = 13.2, 1H, H-6a), 4.03 (dd, *J* = 10.0, 2.8, 1H, H-3), 3.89 (d, *J* = 13.2, 1H, H-6b), 3.87 (d, *J* = 12.0, 1H, H-6*a), 3.87 (m, 1H, H-1a) 3.71 (d, *J* = 11.6, 1H, H-6*b), 3.65 – 3.54 (m, 1H, H-1'a), 3.59 (t, *J* = 5.8 Hz, 2H, H_2-5'), 3.64 - 3.55 (m, 1H, H-1b), 3.28 – 3.17 (m, 1H, H-1'b), 2.01 – 1.86 (m, 1H, H-2'a), 1.86 – 1.77 (m, 1H, H-2'b), 1.78 – 1.70 (m, 2H, H-4'), 1.68 – 1.46 (m, 2H, H-3'). ^{13}C NMR (100 MHz, MeOD) δ 140.5, 137.5 (C_q BiPh), 129.7, 128.7, 128.5, 128.1, 127.0, 126.6, 126.5 (C_{Ar} BiPh), 72.4 (C-5), 72.2 (C-6'), 69.7 (C-3), 69.5 (C-5'), 67.1 (C-4), 65.7 (C-2), 56.2 (C-6*), 55.8 (C-6), 52.8 (C-1), 50.4 (C-1'), 28.7 (C-2'), 25.0 (C-3'), 22.7 (C-4'). $[\alpha]^{20}_D$ = -14.6 (c = 0.34, MeOH). IR/cm^{-1}: 3675, 3323, 2971, 1674, 1407, 1202, 1133, 1076. HRMS: found 446.25345 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

5-*C*-Hydroxymethyl-*N*-butyl-1-deoxy-D-allonojirimycin (121):



9 (0.20 mmol) and butyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **121** (6.2 mg, 0.025 mmol, yield 12%). ^{1}H NMR (600 MHz, MeOD) δ 4.18 (d, *J* = 14.2 Hz, 1H, H-6a), 4.08 (t, *J* = 2.9 Hz, 1H, H-3), 3.97 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.94 – 3.90 (m, 1H, H-2), 3.89 (d, *J* = 12.6 Hz, 1H, H-6*b), 3.89 (d, *J* = 2.7 Hz, 1H, H-4), 3.87 (d, *J* = 14.2 Hz, 1H, H-6b), 3.61 (ddd, *J* = 13.0, 11.9, 5.0 Hz, 1H, H-1'), 3.36 – 3.34 (m, 2H, H_2-1), 1.92 – 1.80 (m, 1H, H-2'a), 1.76 – 1.59 (m, 1H, H-2'b), 1.54 – 1.33 (m, 2H, H_2-3'), 1.01 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (150 MHz, MeOD) δ 72.6 (C-5), 71.8 (C-3), 67.5 (C-4), 65.1 (C-2), 57.0 (C-6), 57.0 (C-6*), 53.0 (C-1'), 49.0 (C-1), 28.4 (C-2'), 21.1 (C-3'), 13.9 (C-4'). $[\alpha]^{20}_D$ = -0.2 (c = 0.12, MeOH). IR/cm^{-1}: 3352, 2970, 2879, 1674, 1430, 1201, 1136, 1056. HRMS: found 250.16502 $[C_{11}H_{23}NO_5+H]^+$, calculated for $[C_{11}H_{23}NO_5+H]^+$ 250.16490.

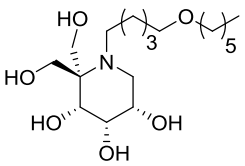
5-*C*-Hydroxymethyl-*N*-nonyl-1-deoxy-D-allonojirimycin (122):



9 (0.20 mmol) and nonyl bromide (0.30 mmol) was subjected to general alkylation procedure with to provide **122** (8.3 mg, 0.026 mmol, yield 13%). ^{1}H NMR (400 MHz, MeOD) δ 4.21 (d, *J* = 14.3 Hz, 1H, H-6a), 4.10 (t, *J* = 2.9 Hz, 1H, H-3), 3.99 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.95 (dd, *J* = 6.5, 3.1 Hz, 1H, H-2), 3.92 (d, *J* = 12.4 Hz, 1H, H-6*b), 3.91 (d, *J* = 2.4 Hz, 1H, H-4), 3.89 (d, *J* = 14 Hz, 1H, H-6b), 3.63 (td, *J* = 12.4, 5.0 Hz, 1H, H-1'a), 3.42 – 3.35 (m, 2H, H_2-1), 3.14 (dt, *J* = 12.5, 6.3 Hz, 1H, H-1'b), 1.98 – 1.66 (m, 2H, H_2-2'), 1.46 – 1.33 (m, 12H, H_2-3' - H_2-8'), 0.94 (t, *J* = 7.1 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 71.2 (C-5), 70.3 (C-3), 66.1 (C-4), 63.7 (C-2), 55.6 (C-6), 55.6 (C-6*), 51.8 (C-1'), 47.5 (C-1), 31.6, 29.1, 28.9, 28.8, 26.4, 25.0, 22.3 (C-2' - C-8'), 13.0 (C-9'). $[\alpha]^{20}_D$ = -0.2 (c = 0.17, MeOH). IR/cm^{-1}: 3352, 2926, 2858, 1670, 1456, 1435, 1379,

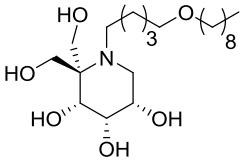
1201, 1134, 1056. HRMS: found 320.24328 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

5-*C*-Hydroxymethyl-*N*-hexyloxypentyl-1-deoxy-D-allonojirimycin (123):



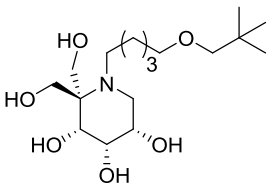
9 (0.20 mmol) and pentyloxyhexyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **123** (5.0 mg, 0.014 mmol, yield 7%). ^{1}H NMR (600 MHz, MeOD) δ 4.21 (d, *J* = 14.2 Hz, 1H, H-6a), 4.10 (t, *J* = 2.8 Hz, 1H, H-3), 3.99 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.96 – 3.93 (m, 2H, H_2-2), 3.91 (d, *J* = 12.4 Hz, 1H, H-6*b), 3.91 (d, *J* = 2.7 Hz, 1H, H-4), 3.89 (d, *J* = 14.3 Hz, 1H, H-6b), 3.68 – 3.59 (m, 1H, H-1'a), 3.48 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.46 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.40 – 3.36 (m, 2H, H_2-1), 3.15 (td, *J* = 12.4, 5.0 Hz, 1H, H-1'b), 1.96 – 1.90 (m, 1H, H-2'a), 1.80 – 1.71 (m, 1H, H-2'b), 1.68 – 1.66 (m, 2H, H_2-4'), 1.60 – 1.56 (m, 2H, H_2-7'), 1.55 – 1.44 (m, 2H, H_2-3'), 1.42 – 1.30 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 6.9 Hz, 3H, H_3-11'). ^{13}C NMR (150 MHz, MeOD) δ 72.3 (C-5), 71.7 (C-6'), 71.4 (C-3), 71.0 (C-5'), 67.1 (C-4), 64.7 (C-2), 56.6 (C-6), 56.6 (C-6*), 52.7 (C-1'), 48.5 (C-1), 31.9 (C-9'), 30.3 (C-7'), 29.8 (C-4'), 26.6 (C-8'), 25.8 (C-2'), 24.2 (C-3'), 23.3 (C-10'), 14.0 (C-11'). $[\alpha]^{20}_D$ = +0.0 (c = 0.10, MeOH). IR/cm^{-1}: 3352, 2929, 2860, 1751, 1676, 1431, 1371, 1205, 1132, 1080. HRMS: found 264.26942 $[C_{18}H_{37}NO_6+H]^+$, calculated for $[C_{18}H_{37}NO_6+H]^+$ 264.26936.

5-*C*-Hydroxymethyl-*N*-nonyloxypentyl-1-deoxy-D-allonojirimycin (124):



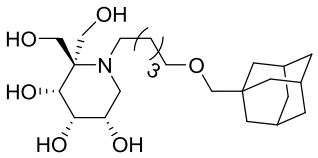
9 (0.20 mmol) and pentyloxynonyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **124** (3.3 mg, 0.008 mmol, yield 4%). ^{1}H NMR (600 MHz, MeOD) δ 4.21 (d, *J* = 14.3 Hz, 1H, H-6a), 4.10 (t, *J* = 2.9 Hz, 1H, H-3), 3.99 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.96 – 3.93 (m, 1H, H-2), 3.91 (d, *J* = 12 Hz, 1H, H-6*b), 3.91 (d, *J* = 2.4 Hz, 1H, H-4), 3.89 (d, *J* = 14.4 Hz, 1H, H-6b), 3.67 – 3.60 (m, 1H, H-1'a), 3.48 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.46 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.39 – 3.33 (m, 2H, H_2-1), 3.15 (td, *J* = 12.5, 5.0 Hz, 1H, H-1'b), 1.99 – 1.88 (m, 1H, H-2'a), 1.84 – 1.72 (m, 1H, H-2'b), 1.68 – 1.66 (m, 2H, H_2-4'), 1.58 (dt, *J* = 8.0, 6.4 Hz, 2H, H_2-7'), 1.55 – 1.45 (m, 2H, H_2-3'), 1.41 – 1.27 (m, 12H, H_2-8' – H_2-13'), 0.93 (t, *J* = 7.1 Hz, 3H, H_3-14'). ^{13}C NMR (150 MHz, MeOD) δ 72.3 (C-5), 71.7 (C-6'), 71.4 (C-3), 71.0 (C-5'), 67.1 (C-4), 64.7 (C-2), 56.6 (C-6), 56.6 (C-6*), 52.7 (C-1'), 49.5 (C-1), 32.7 (C-9'), 30.4 (C-7'), 30.3, 30.2, 30.0 (C-10', C-11', C-12'), 29.8 (C-4'), 26.9 (C-8'), 25.8 (C-2'), 24.2 (C-3'), 23.3 (C-13'), 14.1 (C-14'). $[\alpha]^{20}_D$ = -0.2 (c = 0.07, MeOH). IR/cm^{-1}: 3292, 2924, 2856, 1676, 1425, 1205, 1134, 1055. HRMS: found 406.31623 $[C_{21}H_{43}NO_6+H]^+$, calculated for $[C_{21}H_{43}NO_6+H]^+$ 406.31631.

5-*C*-Hydroxymethyl-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxy-D-allonojirimycin (125):



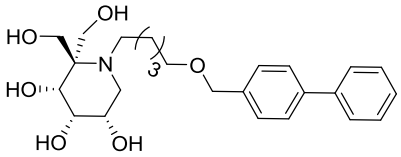
9 (0.20 mmol) and 1-bromo-5-(2,2-dimethyl-1-propoxy)pentane (0.31 mmol) was subjected to general alkylation procedure with to provide **125** (13.8 mg, 0.04 mmol, yield 20%). ^{1}H NMR (400 MHz, MeOD) δ 4.21 (d, *J* = 14.3 Hz, 1H, H-6a), 4.11 (t, *J* = 2.9 Hz, 1H, H-3), 4.00 (d, *J* = 12.1 Hz, 1H, H-6*a), 3.98 – 3.94 (m, 1H. H-2), 3.92 (d, *J* = 12.4 Hz, 1H, H-6*b), 3.92 (d, *J* = 3.2 Hz, 1H, H-4), 3.90 (d, *J* = 14.8 Hz, 1H, H-6b), 3.65 (td, *J* = 12.4, 5.0 Hz, 1H, H-1'a), 3.47 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.42 – 3.38 (m, 2H, H_2-1), 3.22 – 3.13 (m, 1H, H-1'b), 3.10 (s, 2H, H_2-6'), 2.01 – 1.89 (m, 1H, H-2'a), 1.88 – 1.73 (m, 1H, H-2'b), 1.67 (dt, *J* = 7.9, 6.4 Hz, 2H, H_2-4'), 1.58 – 1.48 (m, 2H, H_2-3'), 0.93 (s, 9H, 3 x CH_3). ^{13}C NMR (100 MHz, MeOD) δ 81.1 (C-6'), 71.3 (C-5), 70.6 (C-5'), 70.3 (C-3), 66.2 (C-4), 63.7 (C-2), 55.7, 55.7 (C-6, C-6*), 51.7 (C-1'), 47.2 (C-1), 31.5 (C-7'), 28.9 (C-4'), 25.8 (CH_3), 24.8 (C-2'), 23.3 (C-3'). $[\alpha]^{20}_D$ = -0.3 (c = 0.28, MeOH). IR/cm^{-1}: 3675, 2971, 1672, 1393, 1202, 1066. HRMS: found 350.25347 $[C_{17}H_{35}NO_6+H]^+$, calculated for $[C_{17}H_{35}NO_6+H]^+$ 350.25371.

5-*C*-Hydroxymethyl-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-D-allonojirimycin (126):



9 (0.20 mmol) and 5-(adamantan-1-yl-methoxy)pentyl bromide (0.29 mmol) was subjected to general alkylation procedure to provide **126** (9.5 mg, 0.022 mmol, yield 11%). ^{1}H NMR (400 MHz, MeOD) δ 4.21 (d, *J* = 14.2 Hz, 1H, H-6a), 4.10 (t, *J* = 2.9 Hz, 1H, H-3), 3.98 (d, *J* = 12.4 Hz, 1H, H-6*a), 3.96 – 3.92 (m, 1H, H_2-2), 3.91 (d, *J* = 12.4 Hz, 1H, H-6*b), 3.91 (d, *J* = 2.8 Hz, 1H, H-4), 3.90 (d, *J* = 14 Hz, 1H, H-6b), 3.64 (td, *J* = 12.3, 4.9 Hz, 1H, H-1'a), 3.44 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.41 – 3.35 (m, 2H, H_2-1), 3.22 – 3.10 (m, 1H, H-1'b), 1.97 (t, *J* = 3.2 Hz, 3H, 3 x CH ada), 1.97 – 1.90 (m, 1H, H_2-2'a), 1.80 – 1.68 (m, 6H, 3 x CH_2 ada), 1.74 – 1.69 (m, 1H, H-2'b), 1.70 – 1.62 (m, 2H, H_2-4'), 1.59 (d, *J* = 2.9 Hz, 6H, 3 x CH_2 ada), 1.56 – 1.44 (m, 2H, H-3'). ^{13}C NMR (100 MHz, MeOD) δ 81.7 (C-6'), 71.3 (C-5), 70.7 (C-5'), 70.3 (C-3), 66.1 (C-4), 63.7 (C-2), 55.6 (C-6), 55.6 (C-6*) 51.7 (C-1'), 48.3 (C-1), 39.4 (CH_2 ada), 36.9 (CH_2 ada), 33.8 (C_q ada), 28.8 (C-4'), 28.3 (CH ada), 24.8 (C-2'), 23.3 (C-3'). $[\alpha]^{20}_{D}$ = -0.1 (c = 0.19, MeOH). IR/cm^{-1}: 3675, 2988, 1673, 1394, 1205, 1131, 1066. HRMS: found 428.30043 $[C_{23}H_{41}NO_6+H]^+$, calculated for $[C_{23}H_{41}NO_6+H]^+$ 428.30066.

5-*C*-Hydroxymethyl-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxy-D-allonojirimycin (127):



9 (0.20 mmol) and (biphenyl-4-yl-methoxy)pentyl bromide (0.30 mmol) was subjected to general alkylation procedure to provide **127** (2.8 mg, 0.0062 mmol, yield 3%). ^{1}H NMR (600 MHz, MeOD) δ 7.65 – 7.57 (m, 4H, H_{Ar} BiPh), 7.43 (d, *J* = 8.0 Hz, 4H, H_{Ar} BiPh), 7.34 (d, *J* = 7.4 Hz, 1H, H_{Ar} BiPh), 4.56 (s, 2H, H-6'), 4.17 (d, *J* = 14.3 Hz, 1H, H-6a), 4.07 (t, *J* = 2.9 Hz, 1H, H-3), 3.96 (d, *J* = 12.2 Hz, 1H, H-6b), 3.92 – 3.89 (m, 1H, H-2), 3.90 (d, *J* = 14.4 Hz, 1H, H-6*a), 3.88 (d, *J* = 3 Hz, 1H, H-4), 3.86 (d, *J* = 13.8 Hz, 1H, H-6*b), 3.64 – 3.59 (m, 1H, H-1'a), 3.56 (t, *J* = 3.56, 2H, H_2-5'), 3.37 – 3.32 (m, 2H, H_2-1), 3.17 – 3.10 (m, 1H, H-1'b), 1.97 – 1.88 (m, 1H, H-2'a), 1.80 – 1.73 (m, 1H, H-2'b), 1.74 – 1.68 (m, 2H, H_2-4'), 1.59 – 1.46 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 142.1, 141.9 (C_q Bn), 138.8, 129.9, 129.4, 128.4, 128.0, 127.9 (C_{Ar} BiPh), 73.7 (C-6'), 71.8 (C-3), 71.0 (C-5'), 67.5 (C-4), 65.1 (C-2), 62.6 (C-5), 57.0 (C-6), 56.9 (C-6*), 53.1 (C-1'), 49.9 (C-1), 30.2 (C-4'), 26.2 (C-2'), 24.7 (C-3'). $[\alpha]^{20}_{D}$ = +0.54 (c = 0.06, MeOH). IR/cm^{-1}: 3337, 2928, 2863, 1738, 1673, 1442, 1365, 1205, 1130. HRMS: found $[C_{25}H_{35}NO_6+H]^+$ 446.25357, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

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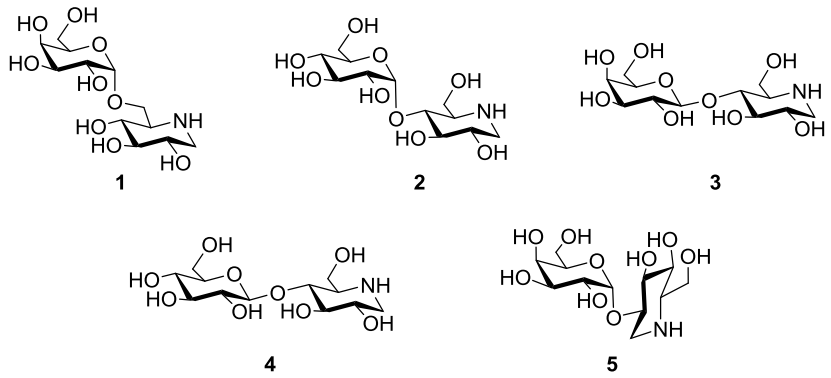
7 Summary, Work in Progress and Future Prospects

This Thesis describes the design, synthesis and evaluation as glycoprocessing enzyme inhibitors of focused libraries of iminosugars. In the studies described, 1-deoxynojirimycin (DNJ), the archetypal iminosugar, and its known *N*-alkylated derivatives, served as starting points. DNJ modifications presented here include alteration of the substitution pattern of the piperidine core structure; variation in the N substituent, or a combination of the two. Biological evaluation of the synthesized compounds focused on the glycoprocessing enzymes involved in glucosylceramide metabolism: glucosylceramide synthase (GCS), lysosomal glucosylceramidase (GBA1) and neutral glucosylceramidase (GBA2), and in all examples presented the inhibitory potency of newly synthesized compounds are compared with that of literature compounds.

In **Chapter 1** the current and potential applications of iminosugars in biomedicine are introduced. Given the importance of this class of compounds, numerous synthetic strategies have been reported over the decades, thus allowing the synthesis of natural compounds that are hard to access in large quantities and/or purity from nature, but also to expand the structural diversity. **Chapter 2** reviews some particularly versatile synthetic strategies for the construction of DNJ, including strategies involving a double reductive amination as a key step – a key step that also features in several routes of synthesis as presented in this Thesis.

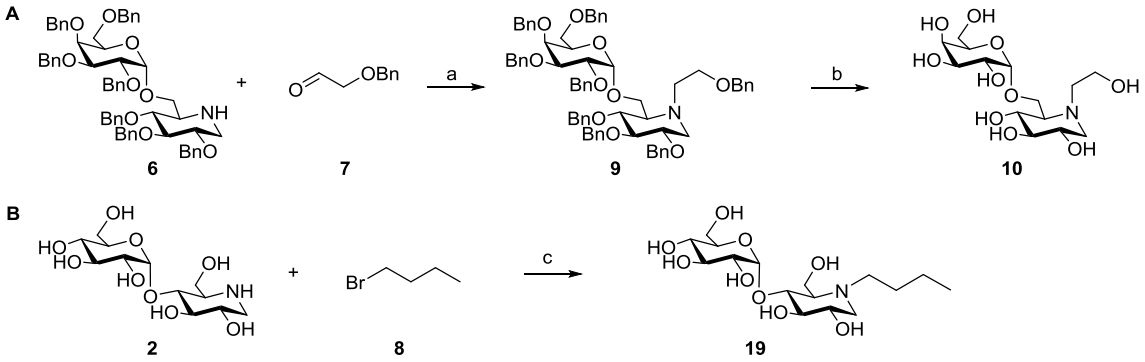
Glycosylated DNJs comprise a relatively less well explored class of iminosugars when compared to monosaccharidic DNJs. In **Chapter 3** an efficient method is described for the synthesis of glycosylated DNJ derivatives starting from the corresponding disaccharides. Five different glycosylated DNJ structures were successfully constructed (**1** – **5**, Figure 1) following a route comprising selective liberation of the anomeric center of the reducing glucose in the starting disaccharides followed by reduction to the diol, oxidation to the 5-keto aldehyde and double reductive amination.

***Figure 1**: Glycosylated 1-deoxynojirimycin (**1** - **5**) constructed in Chapter 3*



N-alkyl derivatives of some of these glycosylated iminosugars (see for the synthesized structures Table 1) were prepared as depicted in scheme 1. As an example, reductive amination of the per-*O*-benzyl protected iminodisaccharide **6** with sodium cyanoborohydride as the reducing agent and including the appropriate aldehyde provides, after global deprotection, hydroxyethyl derivative **10** (Scheme 1A; see for experimental details the experimental section at the end of this Chapter). Alternatively, fully deprotected iminodisaccharide **2** can be subjected to butyl bromide and potassium carbonate in DMF to yield *N*-butyl-iminodisaccharide **19** (Scheme 1B). A combination of both approaches should enable the synthesis of the complete panel as depicted in Table 1.

***Scheme 1**: N-Alkylation strategies of glycosylated DNJ derivatives (**9 - 28**)*



Reagents and conditions: [a] AcOH, $NaCHBH_3$, MeOH, DCM, 64%; [b] Pd/C, H_2, DMF/MeOH, 91%; [c] K_2CO_3, DMF, 85 °C, 58%.

***Table 1**: Code of the synthesized N-alkyl glycosylated DNJ derivatives*

	*Melibio DNJ (**1**)*	*Malto DNJ (**2**)*	*Lacto DNJ (**3**)*	*Cellobio DNJ (**4**)*
N-hydroxyethyl	[a] **9**, [b] **10**	N.S.	N.S.	N.S.
N-butyl	[a] **11**, [b] N.S.	[a] **18**, [b] **19**	N.S.	[c] **23**
N-nonyl	[a] **12**, [b] **13**	[a] **20**, [b] N.S.	N.S.	[c] **24**
N-5-(hexyloxy)pentyl	N.S.	N.S.	[c] **21**	[c] **25**
N-5-(nonyloxy)pentyl	[c] **14**	N.S.	N.S.	[c] **26**
N-(biphenyl-4-yl-methoxy)pentyl	[c] **15**	N.S.	N.S.	[c] **27**
N-5-(adamantan-1-yl-methoxy)pentyl	[c] **16**	N.S.	[c] **22**	N.S.
N-5-(3,3-dimethyl-1-propyloxy)pentyl	[c] **17**	N.S.	N.S.	[c] **28**

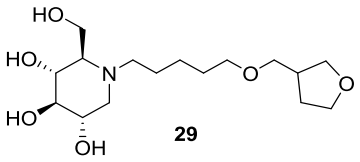
*N.S.: not synthesized or purified.

*[a],[b],[c]: synthesized via conditions a, b or c described in scheme 1.

GBA2 selective inhibitors are desirable commodities both for fundamental biological studies on the physiological role of GBA2 and as potential clinical candidates, in case GBA2 turns out to be a relevant drug target (as is currently considered in relation to the lysosomal storage disorders, Gaucher disease and Niemann-Pick type C disease). Unfortunately, all GBA2

inhibitors described in the literature have overlapping activities on either of the two other GlcCer metabolism relating enzymes, GCS and GBA1. **Chapter 4** discusses the design and synthesis of *N*-alkyl DNJ derivatives as potential GBA2 selective inhibitors. A focused library composed of *N*-pentyloxy neopentyl isosteres iminosugars was built and evaluated, and compound **29** (Figure 2) was found to be the most selective GBA2 inhibitor of the investigated series.

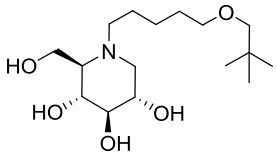
***Figure 2**: Most promising GBA2 selective inhibitor from Chapter 4*



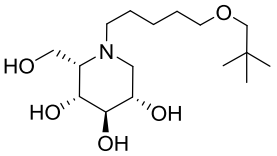
29

Studies on configurational iminosugars have revealed that D-*ido*-configured DNJ derivatives possess remarkable GBA2 selectivity. As depicted in Figure 3, D-*ido*-configured, *N*-alkyl derivative **32** is a low nanomolar GBA2 inhibitor. The compound is even more potent than the known GBA2 inhibitors **30** and **31**, and is also more selective (**32**: $IC_{50\ GCS}/IC_{50\ GBA2}$ 1750, $IC_{50\ GBA1}/IC_{50\ GBA2}$ 92071; **30**: $IC_{50\ GCS}/IC_{50\ GBA2}$ 1020, $IC_{50\ GBA1}/IC_{50\ GBA2}$ 1252).

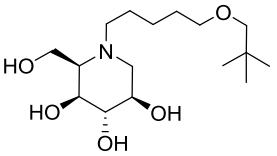
***Figure 3**: Structure and inhibitory activity of D-gluco, L-ido and D-ido iminosugars*



30, D-*gluco* NEO
IC_{50} GCS 5 μM
IC_{50} GBA1 6 μM
IC_{50} GBA2 5 nM



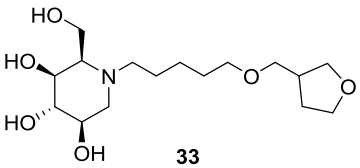
31, L-*ido* NEO
IC_{50} GCS 1.6 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 nM



32, D-*ido* NEO
IC_{50} GCS 7 μM
IC_{50} GBA1 387 μM
IC_{50} GBA2 4 nM

Hence, D-*ido* structural iminosugar is a promising starting point for further research on GBA2 selective inhibitors, for instance by variation of the *N*-alkyl substituent as has been the object of study in **Chapter 4** (leading to, for instance, compound **33**, Figure 4).

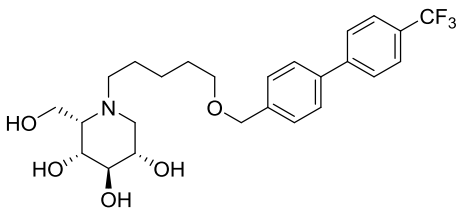
***Figure 4**: Structure of designed GBA2 selective inhibitor*



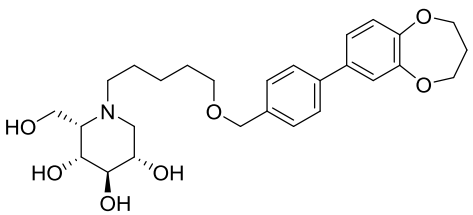
33

Iminosugars with dual GCS/GBA2 inhibitory activity are promising leads for drug development for the treatment of several lysosomal storage disorders. In **Chapter 5**, 16 *N*-alkyl D-glucose configured and L-idose configured DNJ derivatives were designed, synthesized and evaluated on their efficacy as dual GCS/GBA2 inhibitors. Regrettably, no outstanding new inhibitor was identified. Amongst the compounds evaluated, the one carrying a *para*-trifluorometyl substituted *N*-biphenyl moiety (L-*ido*-DNJ **34**) proved to be the most GCS/GBA2 selective compound of the series (selectivity as set against GBA1 inhibitory activity), whereas derivatives with a low logP value (such as **35**) deserve future attention as well because of their suspected improved (compared to **34**) *in vivo* activity.

***Figure 5**: Most promising GCS/GBA2 inhibitors from Chapter 5*



34



35

As also highlighted in **Chapter 5**, future research might focus on modification of the inner benzene moiety of the biphenyl substituent in the L-idose configured and D-glucose configured DNJ derivatives (for instance, **36** – **39**, Figure 6), or even modification of both benzenes (for instance, **40** – **47**).

Chapter 6 discusses the design and synthesis of a focused library comprising four configurational isomeric bis-hydroxymethyl iminosugars (**48** – **51**, Figure 7). These core structures were decorated with different aliphatic chains and the complete library was assessed on their inhibitory potential against GCS, GBA1 and GBA2. The additional (compared to the parent iminosugars) hydroxymethyl group does not bring extra potency and neither selectivity against the target enzymes.

Lack of potency towards the target enzymes may be due to steric factors, and one way to overcome this, but that would keep the symmetrical carbon at C-5 intactly, would be to condense the two hydroxyls to form an oxetane (as in **52** – **55**, Figure 8). Oxetane groups are common functional groups in medicinal chemistry and confer to drugs/drug candidates desirable features including solubility and metabolic stability.

***Figure 6**: Relevant D-gluco and L-idose configured DNJ derivatives carrying a modified biphenyl functional group*

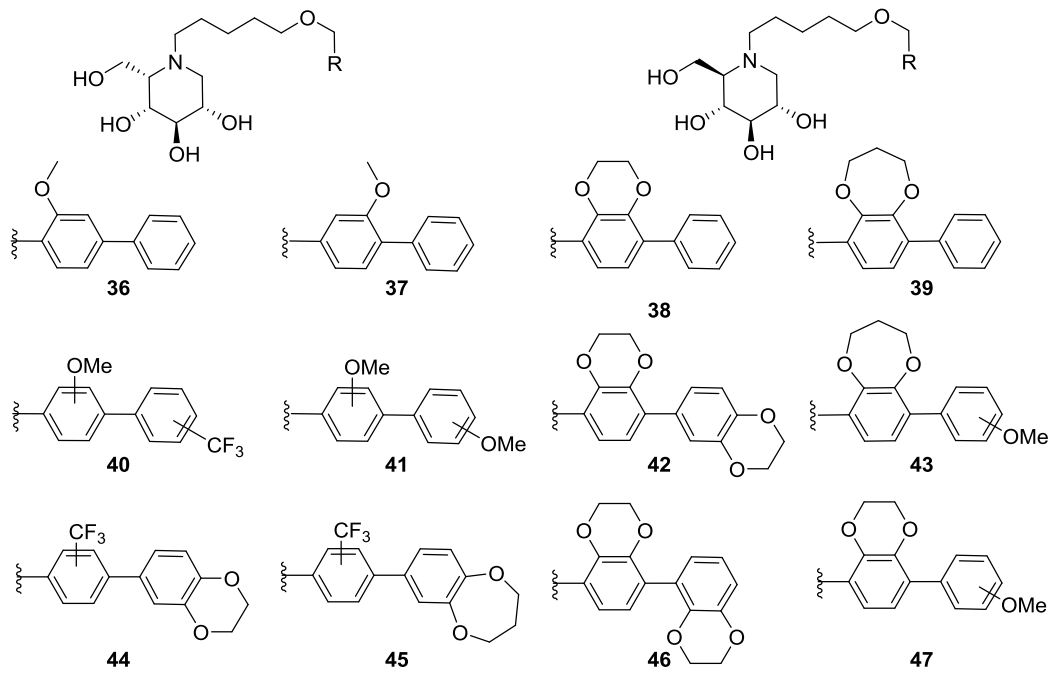


***Figure 7**: 5-Bis-hydroxymethyl DNJ compounds (**48 - 51**) described in Chapter 6*

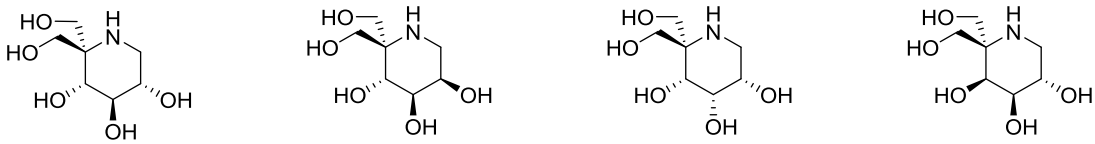
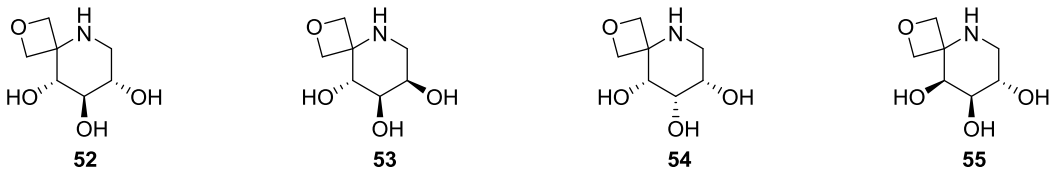
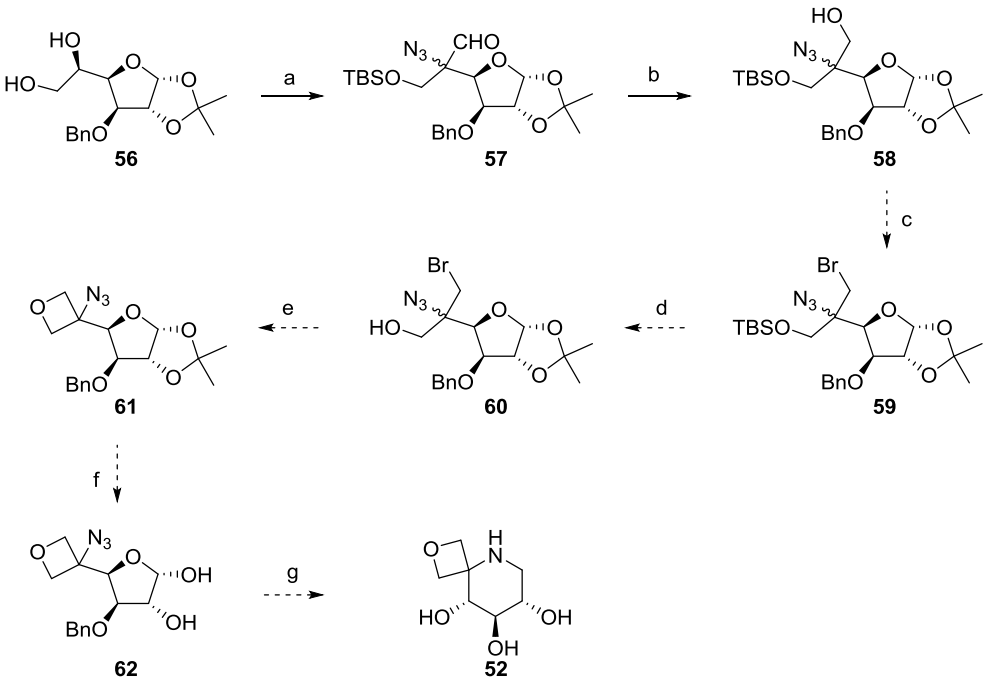


***Figure 8**: Structures of designed C-5 oxetane iminosugars*



***Scheme 2**: Designed synthesis route for 1,5-dideoxy-1,5-imino-5-oxetane-D-xylitol*

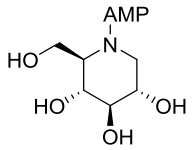


Reagents and conditions: [**a**] 1) TBSCl, TEA, DMAP, DCM; 2) PCC, DCM; 3) LDA, DCM, THF; 4) NaN_3, DMF, 115 °C; [**b**] $NaBH_4$; [**c**] CBr_4, PPh_3, DCM; [**d**] TBAF, THF; [**e**] NaOH, H_2O, MeOH; [**f**] TFA, H_2O; [**g**] H_2, Pd/C.

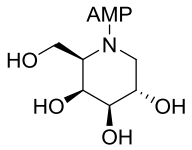
A potential route of synthesis towards compound **52** is presented in Scheme 2. The synthesis is based on diacetone-D-glucose (D-DAG), and standard protecting group manipulations have yielded compound **56**. The additional carbon and nitrogen could be introduced following a strategy similar to that described in **Chapter 6** (from D-DAG to **57**). The newly introduced hydroxylmethyl group (**58**) may be transformed to a bromide via an Appel reaction, and the bromide substituted by the liberated (**59** to **60**) OH-6 to form oxetane (**61**). The anomeric center in **61** is then to be exposed (to give **62**) using the TFA/water system after which reduction of the azide to the amine, reductive amination onto the anomeric aldehyde and concomitant debenzylation should yield **52**.

In previous studies, the inhibitory activity against GCS, GBA1 and GBA2 of a series of 1,2-dideoxynojirimycin derivatives was tested (for example, compounds **67** – **70**, Figure 9). As is evident from the depicted (Figure 9) IC_{50} values, the lack of a C-2 hydroxyl results in a loss of GCS inhibitory activity (compare the GCS inhibitory activity of **63** and **67**; **64** and **68**; **65** and **69**; **66** and **70**, Figure 9), which implies that the existence of a C-2 OH is essential.[1]

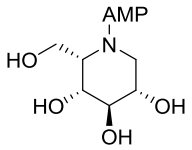
***Figure 9**: IC_{50} values of N-AMP iminosugars*



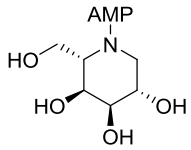
63 IC_{50} GCS 0.2 μM
IC_{50} GBA1 0.5 μM
IC_{50} GBA2 0.8 nM



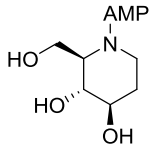
64 IC_{50} GCS 0.14 μM
IC_{50} GBA1 1 μM
IC_{50} GBA2 1 nM



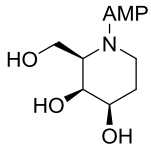
65 IC_{50} GCS 0.1 μM
IC_{50} GBA1 34 μM
IC_{50} GBA2 1 nM



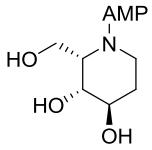
66 IC_{50} GCS 0.2 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.1 μM



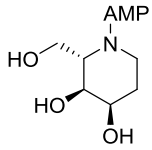
***67** IC_{50} GCS >10 μM
IC_{50} GBA1 10 μM
IC_{50} GBA2 1.0 μM



***68** IC_{50} GCS >10 μM
IC_{50} GBA1 110 μM
IC_{50} GBA2 6.5 μM



***69** IC_{50} GCS >10 μM
IC_{50} GBA1 500 μM
IC_{50} GBA2 0.5 μM

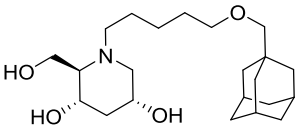


***70** IC_{50} GCS >10 μM
IC_{50} GBA1 200 μM
IC_{50} GBA2 100 μM

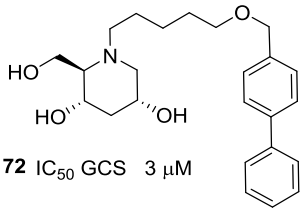
*IC_{50} values are from the literature[1]

In order to investigate the importance of C-3 OH, 1,3-dideoxynojirimycin derivatives have been synthesized and evaluated on their potency to inhibit GCS (e.g. **71** and **72**, Figure 10). It appears that removal of C-3 OH in DNJ (with the remaining chiral centers as in the parent iminosugar, deoxynojirimycin) largely abolishes GCS inhibitory activity (compare GCS inhibitory activity of **71** and **63**, **72** and **89**). It would be useful to have the full set of configurational isomers of **71** (three stereocenters – 6 stereoisomers in total besides **71** and **72**) in hand to establish their inhibitory potency against GCS but also GBA1 and GBA2, and synthetic methodology needs to be developed for this purpose.

***Figure 10**: IC_{50} values of some 1,3-dideoxynojirmmycin derivatives as GCS inhibitors*

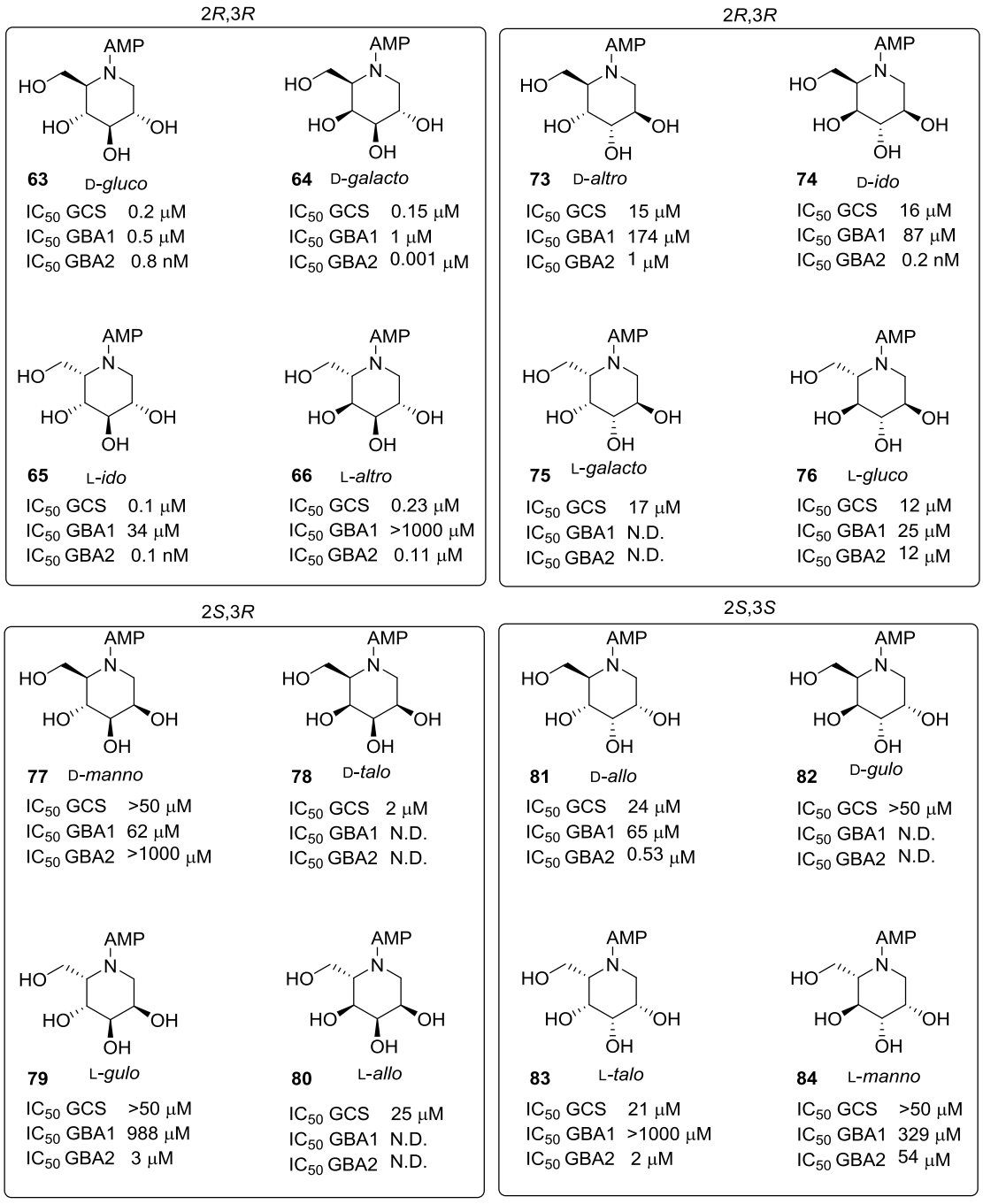


71 IC_{50} GCS ~50 μM



72 IC_{50} GCS 3 μM

***Figure 11**: IC_{50} values of AMP-alkylated DNJ congeners*

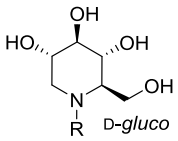


Looking closer at the IC_{50} values obtained for GCS inhibition as described in **Chapter 6**, it becomes apparent that D-glucose configured iminosugars (for instance, **63**, Figure 11) and L-idose configured iminosugars (for instance, **65**) and their C-4 epimers (for instance, D-galactose configured **64** and L-altrose configured **66**) are all able to act as GCS inhibitors. It can thus be concluded that all compounds tested and that display significant GCS inhibitory activity share one common characteristic: the (2*S*, 3*R)* configuration of the diol system (with both hydroxyls present): all relevant GCS inhibitors are found in either the D-glucose, L-idose, D-galactose or L-altrose iminosugar series.

In order to unambiguously confirm this structure-activity-relationship, the efficacy of all 16 DNJ congeners bearing the same *N*-alkyl substituent should be evaluated side-by-side on GCS, GBA1 and GBA2. Initial results towards this goal are presented in Figure 11 and concern some first inhibitory data on the complete set of 16 configurational isomers of *N*-adamantanemethoxypentyl-deoxynojirimycin. It can be seen that D-*gluco* AMP (**63**), L-*ido* AMP (**65**), D-*galacto* AMP (**64**) and L-*altro* AMP (**66**), which all have the (2*S*, 3*R*) configuration, but none of the other configurational isomers, exhibit potent GCS inhibitory activity (0.1 μM - 0.2 μM). The synthesis details of compounds **73**, **74**, **76**, **77**, **79** and **84** can be found in the experimental part.

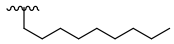
Looking at the inhibition potency of GBA1 and GBA2 as exerted by the 12 configurational isosters introduced in Figure 11, and comparing with the four lead isosteres, D-*ido* derivative **74** stands out as a promising GBA2 selective inhibitor. In order to fully capitalize on the potential of configurational and functional DNJ isosters as selective inhibitors for GCS, GBA or GBA2 as well as for unrelated glycoprocessing enzymes, it would be advantageous to have access to a focused and comprehensive library. Such a library should ideally contain all 16 configurational isomers as well as encompass all alkyl and aryl substituents found on individual DNJ isomers in the literature and that are found to have a beneficial effect, whether on enzyme inhibition potency/selectivity or on pharmacological behavior. Initial synthesis efforts have been conducted towards this goal and the resulting configurational and functional DNJ derivatives – alongside with initial GCS/GBA1/GBA2 inhibitory properties such as have been established yet – are presented in Figures 12 – 15 (see for synthesis details the experimental section).

***Figure 12**: IC_{50} values of DNJ derivatives with 2S, 3R configuration*

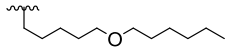


85 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 754 μM
IC_{50} GBA2 20 μM

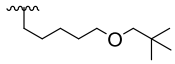
86
IC_{50} GCS 50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.3 μM



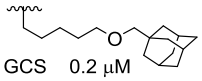
87
IC_{50} GCS 1.5 μM
IC_{50} GBA1 3 μM
IC_{50} GBA2 2 nM



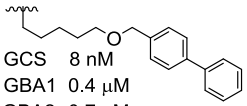
88
IC_{50} GCS 0.08μM
IC_{50} GBA1 5 μM
IC_{50} GBA2 2 nM



30
IC_{50} GCS 5 μM
IC_{50} GBA1 6 μM
IC_{50} GBA2 5 nM

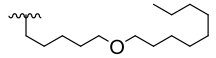


63
IC_{50} GCS 0.2 μM
IC_{50} GBA1 0.5 μM
IC_{50} GBA2 0.8 nM

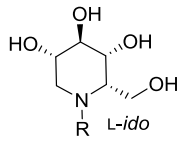


89
IC_{50} GCS 8 nM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 0.7 nM

90
IC_{50} GCS >50 μM
IC_{50} GBA1 37 μM
IC_{50} GBA2 47 nM

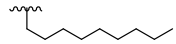


91
IC_{50} GCS 0.07 μM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 1.5 nM

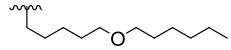


92 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 138 μM

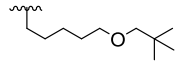
93
IC_{50} GCS 1 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.2 μM



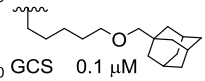
94
IC_{50} GCS 0.1 μM
IC_{50} GBA1 40 μM
IC_{50} GBA2 1 nM



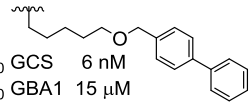
95
IC_{50} GCS 0.03 μM
IC_{50} GBA1 102 μM
IC_{50} GBA2 3 nM



31
IC_{50} GCS 1.6 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 nM

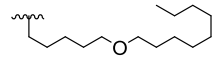


65
IC_{50} GCS 0.1 μM
IC_{50} GBA1 34 μM
IC_{50} GBA2 1 nM

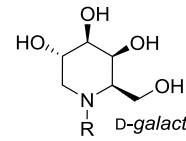


96
IC_{50} GCS 6 nM
IC_{50} GBA1 15 μM
IC_{50} GBA2 1 nM

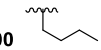
97
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 20 μM



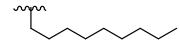
98
IC_{50} GCS 0.015 μM
IC_{50} GBA1 9 μM
IC_{50} GBA2 0.15 nM



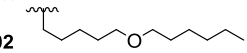
99 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 237 μM
IC_{50} GBA2 11 μM



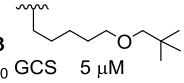
100
IC_{50} GCS 5 μM
IC_{50} GBA1 412 μM
IC_{50} GBA2 30 μM



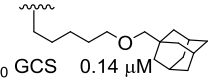
101
IC_{50} GCS 2 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 7.5 nM



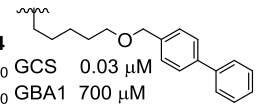
102
IC_{50} GCS 0.3μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 40 nM



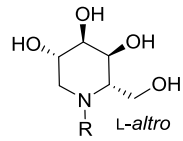
103
IC_{50} GCS 5 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 12 nM



64
IC_{50} GCS 0.14 μM
IC_{50} GBA1 1 μM
IC_{50} GBA2 1 nM

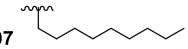


104
IC_{50} GCS 0.03 μM
IC_{50} GBA1 700 μM
IC_{50} GBA2 1 nM

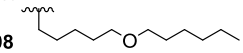


105 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 --- μM

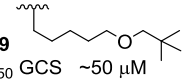
106
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 1.5 μM



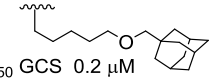
107
IC_{50} GCS 25 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.3 μM



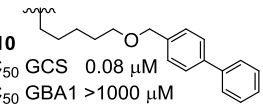
108
IC_{50} GCS 0.5 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.4 μM



109
IC_{50} GCS ~50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.7 μM

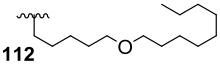


66
IC_{50} GCS 0.2 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.1 μM



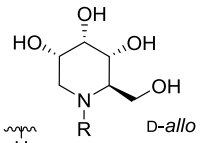
110
IC_{50} GCS 0.08 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 15 nM

111
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 108 μM



112
IC_{50} GCS 0.1μM
IC_{50} GBA1 >100 μM
IC_{50} GBA2 9 nM

***Figure 13**: IC_{50} values of DNJ derivatives with 2S, 3S configuration*



D-*allo*

113 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >100 μM

114
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

115
IC_{50} GCS >50 μM
IC_{50} GBA1 306 μM
IC_{50} GBA2 0.3 μM

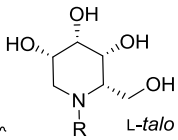
116
IC_{50} GCS >50 μM
IC_{50} GBA1 48 μM
IC_{50} GBA2 >1000 μM

117
IC_{50} GCS >50 μM
IC_{50} GBA1 815 μM
IC_{50} GBA2 17 μM

81
IC_{50} GCS 24 μM
IC_{50} GBA1 65 μM
IC_{50} GBA2 0.5 μM

118
IC_{50} GCS 2.4 μM
IC_{50} GBA1 49 μM
IC_{50} GBA2 0.4 μM

119
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



L-*talo*

120 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >100 μM

121
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 18 μM

122
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 18 μM

123
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 407 μM

124
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 333 μM

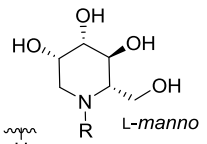
83
IC_{50} GCS 21 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 2 μM

125
IC_{50} GCS 8.5 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 30 μM

126
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 111 μM

127
IC_{50} GCS 19 μM
IC_{50} GBA1 282 μM
IC_{50} GBA2 0.4 μM

128
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >100 μM



L-*manno*

129 R = H
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

130
IC_{50} GCS 2 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 7.5 nM

131
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 4 μM

132
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 361 μM

133
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 21.5 μM

84
IC_{50} GCS >50 μM
IC_{50} GBA1 329 μM
IC_{50} GBA2 55 μM

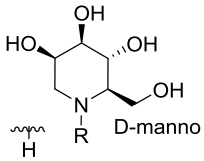
134
IC_{50} GCS 40 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 53 μM

135
IC_{50} GCS 50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

136
IC_{50} GCS >50 μM
IC_{50} GBA1 310 μM
IC_{50} GBA2 16 μM

137
IC_{50} GCS >50 μM
IC_{50} GBA1 29 μM
IC_{50} GBA2 20 μM

***Figure 14**: IC_{50} values of DNJ derivatives with 2R, 3R configuration*

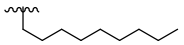


138 H

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 ~100 μM

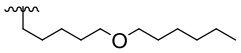
139

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



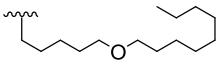
140

IC_{50} GCS >50 μM
IC_{50} GBA1 241 μM
IC_{50} GBA2 >1000 μM



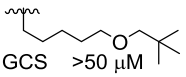
141

IC_{50} GCS 8 μM
IC_{50} GBA1 929 μM
IC_{50} GBA2 3 μM



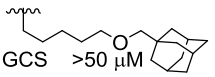
142

IC_{50} GCS >50 μM
IC_{50} GBA1 110 μM
IC_{50} GBA2 31 μM



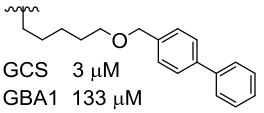
143

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



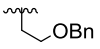
77

IC_{50} GCS >50 μM
IC_{50} GBA1 62 μM
IC_{50} GBA2 61 μM



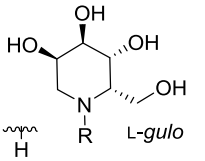
144

IC_{50} GCS 3 μM
IC_{50} GBA1 133 μM
IC_{50} GBA2 --- μM



145

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 151 μM

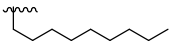


146 H

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM

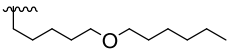
147

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >1000 μM



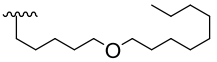
148

IC_{50} GCS >50μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 7.5 μM



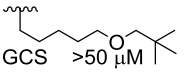
149

IC_{50} GCS 21 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 10 μM



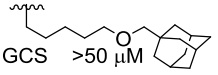
150

IC_{50} GCS 4 μM
IC_{50} GBA1 972 μM
IC_{50} GBA2 2 μM



151

IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 42 μM



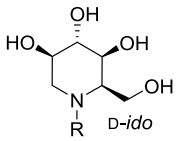
79

IC_{50} GCS >50 μM
IC_{50} GBA1 988 μM
IC_{50} GBA2 3 μM

152

IC_{50} GCS 50 μM
IC_{50} GBA1 19 μM
IC_{50} GBA2 32 μM

***Figure 15**: IC_{50} values of DNJ derivatives with 2R, 3S configuration*



153 H
IC_{50} GCS >50 μM
IC_{50} GBA1 >100 μM
IC_{50} GBA2 >1000 μM

154
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 4 μM

155
IC_{50} GCS 4 μM
IC_{50} GBA1 100 μM
IC_{50} GBA2 10 nM

74
IC_{50} GCS 16 μM
IC_{50} GBA1 88 μM
IC_{50} GBA2 0.2 nM

156
IC_{50} GCS 11 μM
IC_{50} GBA1 2.3 μM
IC_{50} GBA2 2 nM

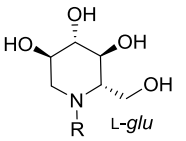
157 OBn
IC_{50} GCS >50 μM
IC_{50} GBA1 98 μM
IC_{50} GBA2 143 μM

158 OH
IC_{50} GCS >50 μM
IC_{50} GBA1 ~100 μM
IC_{50} GBA2 >1000 μM

159
IC_{50} GCS 10 μM
IC_{50} GBA1 25 μM
IC_{50} GBA2 0.7 μM

160
IC_{50} GCS 50 μM
IC_{50} GBA1 32 μM
IC_{50} GBA2 11 μM

32
IC_{50} GCS 7 μM
IC_{50} GBA1 387 μM
IC_{50} GBA2 4 nM



161 H
IC_{50} GCS >50 μM
IC_{50} GBA1 730μM
IC_{50} GBA2 >1000 μM

162
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 >100 μM

163
IC_{50} GCS >50 μM
IC_{50} GBA1 40 μM
IC_{50} GBA2 50 μM

76
IC_{50} GCS 12 μM
IC_{50} GBA1 25.5 μM
IC_{50} GBA2 12 μM

164
IC_{50} GCS 1.4 μM
IC_{50} GBA1 57 μM
IC_{50} GBA2 3 μM

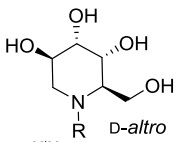
165 OBn
IC_{50} GCS 50 μM
IC_{50} GBA1 ~1000 μM
IC_{50} GBA2 0.3 μM

166 OH
IC_{50} GCS 50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 22 μM

167
IC_{50} GCS 9 μM
IC_{50} GBA1 24 μM
IC_{50} GBA2 4 μM

168
IC_{50} GCS 20 μM
IC_{50} GBA1 429 μM
IC_{50} GBA2 49 μM

169
IC_{50} GCS >50 μM
IC_{50} GBA1 198 μM
IC_{50} GBA2 208 μM



170 H
IC_{50} GCS N.D.
IC_{50} GBA1 N.D.
IC_{50} GBA2 N.D.

171
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 552 μM

172
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 8 μM

73
IC_{50} GCS 15 μM
IC_{50} GBA1 174 μM
IC_{50} GBA2 1 μM

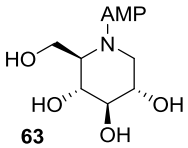
173
IC_{50} GCS >50 μM
IC_{50} GBA1 71 μM
IC_{50} GBA2 6 μM

174 OBn
IC_{50} GCS >50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 126 μM

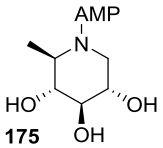
One literature study, describes the synthesis and evaluation of 1,6-dideoxynojirimycin (**175**) and xylose-DNJ (**176**).[1] Compared to DNJ derivative **63** (Figure 16) both compounds

proved to be less potent as GCS inhibitors, with the xylose-configured one less active than the quinuvose-configured one. This result suggests that the functional group at C-6 contributes to GCS inhibitory activity.

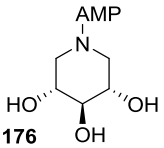
***Figure 16**: IC_{50} values of DNJ-AMP, 6-deoxy-DNJ AMP and 6-dehydroxy-DNJ-AMP*



63
IC_{50} GCS 0.2 μM
IC_{50} GBA1 0.5 μM
IC_{50} GBA2 0.8 nM



175
*IC_{50} GCS 0.8 μM
*IC_{50} GBA1 0.3 μM
*IC_{50} GBA2 30 nM

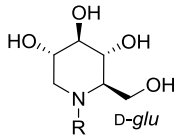


176
*IC_{50} GCS >10 μM
*IC_{50} GBA1 2 μM
*IC_{50} GBA2 800 nM

*IC_{50} data from the literature[1]

Based on the data above, substitution of the C6-OH in **63** with an electron-withdrawing functional group may yield a conceptually new, potent and potentially selective GCS inhibitor. Fluorine is a widely used hydroxyl isostere[2] that has about the same size and is comparatively more electron-withdrawing, and substituting C6-OH in **63** with fluorine therefore appeared an attractive strategy.

***Figure 17**: IC_{50} values of DNJ and 6-deoxy-6-fluoro-DNJ derivatives*



86
IC_{50} GCS 50 μM
IC_{50} GBA1 >1000 μM
IC_{50} GBA2 0.3 μM

87
IC_{50} GCS 1.5 μM
IC_{50} GBA1 3 μM
IC_{50} GBA2 2 nM

88
IC_{50} GCS 0.08μM
IC_{50} GBA1 5 μM
IC_{50} GBA2 2 nM

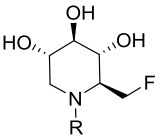
30
IC_{50} GCS 5 μM
IC_{50} GBA1 6 μM
IC_{50} GBA2 5 nM

63
IC_{50} GCS 0.2 μM
IC_{50} GBA1 0.5 μM
IC_{50} GBA2 0.8 nM

89
IC_{50} GCS 8 nM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 0.7 nM

90
IC_{50} GCS >50 μM
IC_{50} GBA1 37 μM
IC_{50} GBA2 47 nM

91
IC_{50} GCS 0.07 μM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 1.5 nM



177
IC_{50} GCS 34 μM
IC_{50} GBA1 298 μM
IC_{50} GBA2 2 μM

178
IC_{50} GCS 13 μM
IC_{50} GBA1 2 μM
IC_{50} GBA2 16 nM

179
IC_{50} GCS 1 μM
IC_{50} GBA1 2.5 μM
IC_{50} GBA2 31 nM

180
IC_{50} GCS 9 μM
IC_{50} GBA1 10 μM
IC_{50} GBA2 68 nM

181
IC_{50} GCS 1.5 μM
IC_{50} GBA1 1 μM
IC_{50} GBA2 4 nM

182
IC_{50} GCS 0.4 μM
IC_{50} GBA1 1 μM
IC_{50} GBA2 5 nM

183
IC_{50} GCS 34 μM
IC_{50} GBA1 298 μM
IC_{50} GBA2 2 μM

184
IC_{50} GCS 0.7 μM
IC_{50} GBA1 0.8 μM
IC_{50} GBA2 7 nM

However, 6-deoxy-6-fluoro-AMP-DNJ (**181**, Figure 17) turned out to be a comparatively poor GCS inhibitor. The same trend is reflected in some *N*-alkyl derivatives when looking at a

side-by-side comparison (compare compounds **177** – **183** with their 6-hydroxy counterparts) and GBA1/GBA2 inhibition potency appears affected by the OH-to-F substitution as well. A tentative conclusion may be that the hydrogen-bond-donating properties of the C6-OH (and not so much the hydrogen-bond accepting properties – though arguably a fluorine partakes in neither) are what makes DNJ derivatives bearing this substituent more potent against the three enzymes tested. Nevertheless, the developed methodology to introduce a fluorine at C-6 allows for synthesis of C6-fluorine-modified, configurational DNJ isomers as well, and it may well be that the O6-for-F substitution is beneficial for DNJ derivatives targeting glycoprocessing enzymes other than the ones subject of this Thesis.

Experimental Section

Enzyme inhibition assays: The inhibitory potencies (IC_{50} values) of the final compounds for GCS, GBA1 and GBA2 were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[3] Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbeliferyl-β-D-glucoside as substrate.[4] Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and 0.2% (w/v) sodium taurocholate. Assays performed in triplicate were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm.

GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with the 4-methylumbeliferyl-β-D-glucoside as substrate.[4] GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbeliferyl-β-D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz) or Bruker 600 (600/150 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[5] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ =589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer provided by GE-Healthcare polymere HW-40S from Toyopearl, column size d = 26 mm; l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 μm, 19 x 150 mm column).

General Procedure A: Alkylation of iminosugars. To a mixture of the 1-bromo-5-alkyloxy-pentane (1.5 eq) and di-isopropylethylamine (DiPEA, 3 eq) was added a solution of iminosugar (1 eq) in DMF (0.2M). The reaction mixture was stirred overnight at 70 °C. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified using silica gel column chromatography (0% → 20% methanol in DCM + 1% NH_4OH).

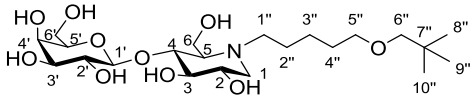
General Procedure B: Alkylation of iminosugars. To a mixture of the bromide chain (1.5 eq) and K_2CO_3 (3eq) was added a solution of the (glycosylated) iminosugar (1eq) in DMF (0.2 M). The reaction suspension was stirred at 85 °C for 18 hours. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified with HPLC.

General Procedure C: Alkylation of protected glycosylated iminosugars. Glycosylated disaccharide iminosugar (0.2 mmol), aldehyde chain (0.3 mmol), AcOH (1.6 mmol), $NaCNBH_3$ (0.8 mmol), Na_2SO_4 (desiccant) and MeOH (2 mL) was mixed at 0 °C and stirred overnight, allowing the temperature to reach r.t. After TLC analysis showed the completely consumption of starting material (4:1, PE:EtOAc), the mixture was filtered and concentrated. The residue was dissolved in DCM (15 mL) and washed with aq. $NaHCO_3$ (10%), dried (Na_2SO_4), filtered and concentrated. The residue was purified using silica gel column chromatography (19:1 → 9:1→ 17:3 → 4:1, PE:EtOAc).

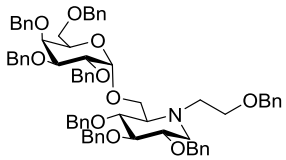
General Procedure D: Catalytic Hydrogenation of protected glycosylated *N*-alkyl DNJ. Protected glycosylated DNJ derivative (1eq) was dissolved in MeOH/DMF (1 mM, 2:1; v:v), and the solution was flushed with argon (3 x). After which a catalytic amount of Pd/C (20%) was added. The mixture was kept shaking under H_2 atmosphere (4 bar) overnight. After TLC analysis showed the absent of benzyl groups, the crude product was purified on size-exclusion column.

Synthesis of alkylated glycosylated-1-deoxynojirimycin

***Figure 18**: Proton and carbon NMR numbering of N-alkylated glycosylated iminosugars:*

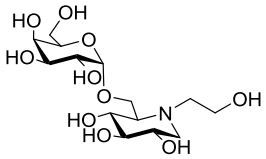


2,3,4-Tri-O-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-*N*-ethan-2-(benzyloxy)-1-deoxynojirimycin (9):



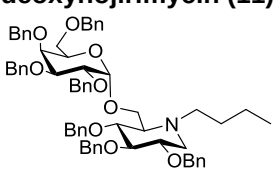
A mixture of DCM/MeOH (1:1, v:v, 15 mL) and *melibio*-DNJ (0.19 g, 0.20 mmol) was cooled in an ice bath. AcOH (92 µL, 1.6 mmol, 8 eq in 1 mL MeOH), 2-(benzyloxy)acetaldehyde (48.1 mg, 0.32 mmol, 1.6 eq in 1 mL DCM) and $NaCNBH_3$ (50.3 mg, 0.8 mmol, 4 eq) were added in respective order. The mixture was stirred overnight allowing warming up to r.t. After evaporating the volatiles, DCM (20 mL) was added to the residue and the organic layer was washed with sat. aq. $NaHCO_3$ (15 mL), dried (Na_2SO_4) filtered and concentrated. The residue was purified on silica gel column (9:1 → 4:1, PE:EtOAc) to gain **9** in 64% yield (140 mg, 0.128 mmol). R_F = 0.54 (7:3, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.11 (m, 40H, H_{Ar} Bn), 4.99 (d, *J* = 3.9 Hz, 1H, H-1'), 4.96 – 4.23 (m, 16H, 8 x CH_2 Bn), 4.02 (dd, *J* = 9.3, 3.5 Hz, 1H, H-2'), 3.98 – 3.83 (m, 5H, H-3', H-4, H-4, H_2-6'), 3.61 – 3.47 (m, 6H, H-2, H_2-2", H-3, H-5', H-6a), 3.43 (dd, *J* = 9.0, 5.7 Hz, 1H, H-6b), 3.20 (dd, *J* = 11.5, 4.5 Hz, 1H, H-1a), 3.03 (dt, *J* = 11.0, 5.5 Hz, 1H, H-1"a), 2.89 (dt, *J* = 14.2, 5.2 Hz, 1H, H-1"b), 2.53 (d, *J* = 7.4 Hz, 1H, H-5), 2.32 (t, *J* = 10.8 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 – 138.1 (C_q Bn), 128.6 – 127.5 (CH_{Ar} Bn), 98.3 (C-1'), 87.3 (C-3), 78.6 (C-2), 78.5 (C-4), 76.7 (C-2'), 75.4, 75.2 (2 x CH_2 Bn), 75.0 (C-3'), 74.9, 73.5, 73.1, 73.1, 72.9, 72.8 (6 x CH_2 Bn), 69.9 (C-4'), 68.8 (C-6), 67.6 (C-2"), 65.7 (C-6'), 64.9 (C-5), 55.2 (C-1), 52.0 (C-1"). $[\alpha]^{20}_D$ = +31.8 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 3029, 2911, 2852, 1496, 1453, 1321, 1207, 1093, 1061, 1027.

6-*O*-(α-D-Galactopyranosyl)-*N*-hydroxyethyl-1-deoxynojirimycin (10):



9 (0.13 g, 0.12 mmol) was subjected to the general procurer D to generate **10** (40.1 mg, 0.109 mmol) in a yield of 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, *J* = 3.6 Hz, 1H, H-1'), 4.30 (d, *J* = 11.0 Hz, 1H, H-6a), 4.17 (dd, *J* = 10.9, 1.8 Hz, 1H, H-6b), 3.92 (d, *J* = 2.7 Hz, 1H, H-4'), 3.85 (t, *J* = 6.1 Hz, 1H, H-5'), 3.78 (dd, *J* = 10.1, 3.0 Hz, 1H, H-2'), 3.75 (dd, *J* = 7.4, 3.6 Hz, 2H, H_2-2"), 3.73 (dd, *J* = 7.5, 4.0 Hz, 1H, H-3'), 3.70 (dd, *J* = 6.0, 3.1 Hz, 2H, H_2-6'), 3.64 (dd, *J* = 10.9, 2.2 Hz, 1H, H-6a), 3.52 (ddd, *J* = 10.6, 9.4, 4.9 Hz, 1H, H-2), 3.43 (t, *J* = 9.4 Hz, 1H, H-4), 3.18 (t, *J* = 9.1 Hz, 1H, H-3), 3.15 (dd, *J* = 11.5, 4.8 Hz, 1H, H-1b), 2.96 (dt, *J* = 13.7, 6.2 Hz, 1H, H-1b"), 2.78 (dt, *J* = 13.9, 5.7 Hz, 1H, H-1a"), 2.46 (dd, *J* = 9.7, 2.4 Hz, 1H, H-5), 2.43 (dd, *J* = 11.4, 10.7 Hz, 1H, H-1a). ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.3 (C-1'), 80.4 (C-3), 72.4 (C-5'), 71.7 (C-2'), 71.4 (C-4), 70.9 (C-4'), 70.7 (C-3'), 70.6 (C-2), 66.1 (C-5), 63.6 (C-6), 62.5 (C-6'), 58.8 (C-2"), 58.3 (C-1), 55.0 (C-1"). $[\alpha]^{20}_D$ = +68.4 (c = 0.5, MeOH). IR/cm^{-1}: 3256, 2894, 1558, 1409, 1343, 1151, 1081, 1038. HRMS: found 370.17082 $[C_{14}H_{28}NO_{10}+H]^+$, calculated for $[C_{14}H_{28}NO_{10}+H]^+$ 370.17077.

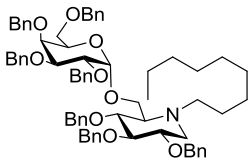
2,3,4-Tri-O-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-*N*-butyl-1-deoxynojirimycin (11).



Protected *melibio*-DNJ (0.19 g, 0.2 mmol) was subjected to the general procedure C to generate **11** (0.18 g, 0.18 mmol) in a yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.14 (m, 35H, H_{Ar} Bn), 5.03 (d, *J* = 3.2 Hz, 1H H-1'), 4.99 – 4.27 (m, 14H, 7 x CH_2 Bn), 4.04 (dd, *J* =

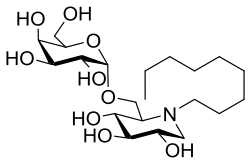
10.2, 2.8 Hz, 1H, H-2'), 4.00 – 3.92 (m, 3H, H-3', H-4', H-5'), 3.89 (dd, *J* = 11.8, 3.4 Hz, 1H, H-6a), 3.83 (dd, *J* = 11.7, 1.5 Hz, 1H, H-6b), 3.62 – 3.42 (m, 5H, H-2, H-3, H-4, H_2-6'), 3.08 (dd, *J* = 11.3, 4.6 Hz, 1H, H-1a), 2.78 (m, 1H, H-1"a), 2.55 (m, 1H, H-1"a), 2.39 (d, *J* = 9.3 Hz, 1H, H-5), 2.15 (t, *J* = 10.7, 1H, H-1"b), 1.32 – 1.42 (m, 2H, H_2-2"), 1.15 – 1.25 (m, 2H, H_2-3"), 0.85 (t, *J* = 7.3 Hz, 3H, H_3-4"). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 – 138.1 (7 x C_q Bn), 128.5 – 127.5 (CH_{Ar} Bn), 98.2 (C-1'), 87.4 (C-3), 78.8 (C-4), 78.8 (C-2), 78.7 (C-3'), 76.8 (C-2'), 75.3 (CH_2 Bn), 75.2 (C-4'), 74,9, 73.5, 73.0, 72.8, (CH_2 Bn), 69.9 (C-5'), 68.9 (C-6'), 65.0 (C-5), 65.0 (C-6), 54.4 (C-1), 52.8 (C-1"), 26.6 (C-2"), 20.8 (C-3"), 14.2 (C-4"). $[\alpha]^{20}_D$ = +11.8 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 3030, 2924, 2870, 1497, 1454, 1362, 1207, 1092, 1059, 1028. HRMS: found 1012.53571 $[C_{21}H_{41}NO_9+H]^+$, calculated for $[C_{21}H_{41}NO_9+H]^+$ 1012.53581.

2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-*N*-nonyl-1-deoxynojirimycin (12):



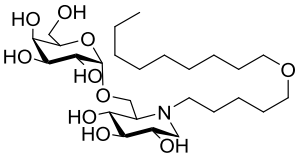
Protected *melibio*-DNJ (0.19 g, 0.2 mmol) was subjected to the general procedure C to generate **12** (0.20 g, 0.19 mmol) in a yield of 93%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 35H, H_{Ar} Bn), 5.75 (d, *J* = 3.3 Hz, 1H, H-1'), 5.03 – 4.23 (m, 14H, 7 x CH_2 Bn), 4.11 (t, *J* = 8.2 Hz, 1H, H-4'), 3.99 (t, *J* = 9.2 Hz, 1H, H-4), 3.83 – 3.57 (m, 6H, H-2', H-3, H-3', H-5', H-6a, H-6'a), 3.56 – 3.48 (m, 3H, H-2, H-6b, H-6'b), 3.08 (dd, *J* = 11.1, 4.7 Hz, 1H, H-1'a), 2.58 – 2.48 (m, 3H, H_2-1", H-5), 2.33 (t, *J* = 10.7 Hz, 1H, H-1'b), 1.47 – 1.15 (m, 12H, H_2-2" – H_2-7"), 1.12 – 1.02 (m, 2H, H_2-8"), 0.89 (t, *J* = 6.9 Hz, 3H, H_3-9"). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.1 – 137.8 (C_q Bn), 128.4 – 126.8 (CH_{Ar} Bn), 95.8 (C-1'), 86.3 (C-3), 82.1 (C-4), 79.7 (C-2), 78.6 (C-3'), 77.7 (C-2'), 75.6, 74.9, 73.6, 73.0, 72.9, 72.8, 72.4 (7 x CH_2 Bn), 72.1 (C-4'), 70.9 (C-5'), 68.2 (C-6'), 65.8 (C-6), 63.0 (C-5), 53.4 (C-1), 52.6 (C-1"), 32.0, 29.6, 29.6, 29.3, 27.4, 24.1, 22.8, 14.2 (C-2'' – C-9''). $[\alpha]^{20}_D$ = +30.4 (c = 2.1, $CHCl_3$). IR/cm^{-1}: 3063, 3030, 2922, 2855, 1497, 1454, 1359, 1207, 1091, 1059, 1028.

6-*O*-(α-D-Galactopyranosyl)-*N*-nonyl-1-deoxynojirimycin (13):



12 was subjected to the general procedure D to generate **13** (25.4 mg, 0.06 mmol) in a yield of 89%. ^{1}H NMR (400 MHz, MeOD) δ 4.92 (d, *J* = 3.9 Hz, 1H, H-1'), 4.33 (d, *J* = 11.7 Hz, 1H, H-6a), 3.91 (d, *J* = 3.5 Hz, 1H, H-3'), 3.89 (d, *J* = 3.8 Hz, 1H, H-2'), 3.81 (t, *J* = 5.9 Hz, 1H, H-5'), 3.74 (d, *J* = 3.3 Hz, 1H, H-4'), 3.71 (d, *J* = 6.0 Hz, 2H, H_2-6'), 3.68 (dd, *J* = 10.6, 5.8 Hz, 1H, H-6b), 3.67 (t, *J* = 11.6 Hz, 1H, H-2), 3.62 (t, *J* = 9.8 Hz, 1H, H-4), 3.54 (dd, *J* = 12.1, 4.8 Hz, 1H, H-1a), 3.37 (t, *J* = 9.2 Hz, 1H, H-3), 3.33 – 3.29 (m, 1H, H-1''a), 3.26 (d, *J* = 10.0 Hz, 1H, H-5), 3.13 (td, *J* = 12.5, 5.5 Hz, 1H, H-1''b), 3.03 (t, *J* = 11.7 Hz, 1H, H-1b), 1.77 – 1.71 (m, 2H, H_2-2''), 1.46 – 1.22 (m, 12H, H_2-3'', H_2-4', H_2-5'', H_2-6'', H_2-7'', H_2-8''), 0.91 (t, *J* = 7.0 Hz, 3H, H_3-9''). ^{13}C NMR (100 MHz, MeOD) δ 100.0 (C-1'), 78.2 (C-3), 72.8 (C-5'), 71.3 (C-4'), 70.8 (C-3'), 70.0 (C-2'), 69.0 (C-4), 68.0 (C-2), 66.2 (C-5), 62.5 (C-6'), 60.3 (C-6), 55.1 (C-1), 54.4 (C-1''), 33.0, 30.5, 30.3, 30.3, 27.7, 24.2, 23.7 (C-2''- C-8''), 14.4 (C-9''). HRMS: found 452.28500 $[C_{21}H_{41}NO_9+H]^+$, calculated for $[C_{21}H_{41}NO_9+H]^+$ 452.28541.

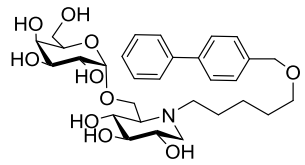
6-*O*-(α-D-Galactopyranosyl)-*N*-[5-(nonyloxy)pentyl]-1-deoxynojirimycin (14):



Melibio-DNJ (**1**, 32.0 mg, 0.1 mmol) was subjected to the general procedure B to generate **14** (16.9 mg, 0.04 mmol) in a yield of 32%. ^{1}H-NMR (400 MHz, MeOD) δ 4.91 (d, *J* = 4.6 Hz, 1H, H-1'), 4.30 (d, *J* = 11.4 Hz, 1H, H-6'a), 3.93 – 3.89 (m, 1H, H-4'), 3.91 – 3.83 (m, 1H, H-4), 3.82 (t, *J* = 6.1 Hz, 1H, H-5'), 3.76 – 3.70 (m, 3H, H_2-6, H-6'b), 3.69 – 3.57 (m, 2H, H-2, H-3'), 3.52 – 3.40 (m, 6H, H_2-1'', H_2-6", H_2-5"), 3.36 (d, *J* = 9.1 Hz, 1H, H-3), 3.28 – 3.20 (m, 1H, H-1a), 3.19 – 3.04 (m, 2H, H-1b, H-5), 1.81 – 1.71 (m, 2H, H_2-2"), 1.68 – 1.60 (m, 2H, H_2-4"), 1.60 – 1.52 (m, 2H, H_2-7"), 1.50 – 1.40 (m, 2H, H_2-3"), 1.33 (m, 12H, H_2-8'', H_2-9'', H_2-10'', H_2-11'', H_2-12'', H_2-13''), 0.90 (t, *J* = 6.8 Hz, 3H, H_3-14").

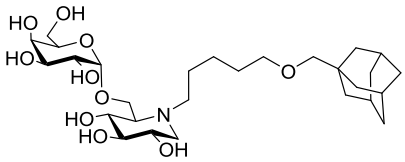
^{13}C NMR (100 MHz, MeOD) δ 100.1 (C-1'), 78.3 (C-3), 72.7 (C-5'), 72.1 (C-6''), 71.5 (C-5''), 71.3 (C-2'), 70.8 (C-4), 70.1 (C-4'), 69.3 (C-3'), 68.3 (C-2), 66.0 (C-5), 62.5 (C-6), 60.6 (C-6'), 55.3 (C-1''), 54.3 (C-1), 33.1, 30.8, 30.7, 30.6, 30.4, 30.2, 27.3, 24.6, 23.9, 23.7 (C-2'' – C-4'', C-7'' – C-13''), 14.5 (C-14''). $[\alpha]^{20}_D$ = +48.2 (c = 0.34, MeOH). IR/cm^{-1}: 3350, 2926, 2855, 1672, 1458, 1431, 1366, 1204, 1134, 1080, 1042. HRMS: found 538.35812 $[C_{26}H_{51}NO_{10}+H]^+$, calculated for $[C_{26}H_{51}NO_{10}+H]^+$ 538.35857.

6-*O*-(α-D-Galactopyranosyl)-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxynojirimycin (15):



Melibio-DNJ (**1**) was subjected to the general procedure A to generate **15** (7.5 mg, 0.01 mmol) in a yield of 13%. ^{1}H NMR (600 MHz, MeOD) δ 7.64 – 7.62 (m, 4H, H_{Ar} BiPh), 7.48 – 7.43 (m, 4H, H_{Ar} BiPh), 7.38 – 7.33 (m, 1H, H_{Ar} BiPh), 4.94 (d, *J* = 4.0 Hz, 1H, H-1'), 4.57 (s, 2H, H_2-6''), 4.33 (d, *J* = 11.7 Hz, 1H, H-6'a), 3.93 (d, *J* = 2.8 Hz, 1H, H-4), 3.91 (dd, *J* = 10.0, 3.9 Hz, 1H, H-4'), 3.83 (t, *J* = 6.1 Hz, 1H, H-5'), 3.75 (dd, *J* = 10.1, 3.4 Hz, 1H, H-2'), 3.73 (d, *J* = 6.0 Hz, 2H, H_2-6), 3.69 (dd, *J* = 11.7, 2.8 Hz, 1H, H-6'b), 3.70 – 3.66 (m, 1H, H-2), 3.64 (dd, *J* = 10.3, 9.2 Hz, 1H, H-3'), 3.59 (t, *J* = 6.2 Hz, 2H, H-5''), 3.55 (dd, *J* = 12.1, 4.9 Hz, 1H, H-1a), 3.38 (t, *J* = 9.2 Hz, 1H, H-3), 3.37 – 3.34 (m, 1H, H-1''a), 3.27 (d, *J* = 11.1 Hz, 1H, H-5), 3.17 (td, *J* = 12.5, 5.1 Hz, 1H, H-1''b), 3.05 (t, *J* = 11.8 Hz, 1H, H-1b), 1.91 – 1.76 (m, 2H, H_2-2''), 1.76 – 1.69 (m, 2H, H_2-4''), 1.58 – 1.49 (m, 2H, H_2-3''). ^{13}C NMR (150 MHz, MeOD) δ 140.6 – 126.4 (C_{Ar}), 98.6 (C-1'), 76.8 (C-3), 72.3 (C-6''), 71.3 (C-5'), 69.8 (C-2'), 69.6 (C-5''), 69.3 (C-4), 68.6 (C-4'), 67.6 (C-3'), 66.5 (C-2), 64.7 (C-5), 61.1 (C-6), 58.9 (C-6'), 53.7 (C-1), 52.9 (C-1''), 28.7 (C-4''), 23.2 (C-3''), 22.5 (C-2''). $[\alpha]^{20}_D$ = +41.4 (c = 0.5, MeOH); IR/cm^{-1}: 3550, 3062, 2302, 1716, 1699, 1558, 1521, 1506, 1489, 1394, 1338, 1203, 1139, 1080, 1064, 1039. HRMS: found 578.29407 $[C_{30}H_{43}NO_{10}+H]^+$, calculated for $[C_{30}H_{43}NO_{10}+H]^+$ 578.29597.

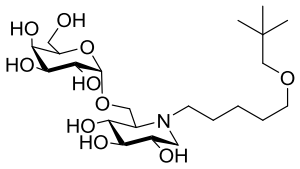
6-*O*-(α-D-Galactopyranosyl)-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (16):



Melibio-DNJ (**1**) was subjected to the general procedure A to generate **16** (5.6 mg, 0.01 mmol) in a yield of 10%**.** ^{1}H NMR (600 MHz, MeOD) δ 4.95 (d, *J* = 3.9 Hz, 1H, H-1'), 4.35 (d, *J* = 11.7 Hz, 1H, H-6'a), 3.94 (dd, *J* = 3.4, 1.0 Hz, 1H, H-4), 3.91 (dd, *J* = 10.0, 3.9 Hz, 1H, H-4'), 3.83 (t, *J* = 6.1 Hz, 1H, H-5'), 3.76 (dd, *J* = 10.1, 3.3 Hz, 1H, H-2'), 3.73 (d, *J* = 6.1 Hz, 2H, H_2-6), 3.72 – 3.67 (m, 2H, H-6'b, H-2), 3.65 (t, *J* = 9.9 Hz, 1H, H-3), 3.56 (dd, *J* = 12.1, 4.9 Hz, 1H, H-1a), 3.44 (t, *J* = 6.2 Hz, 2H, H_2-5''), 3.39 (t, *J* = 9.3 Hz, 1H, H-3), 3.36 – 3.34 (m, 1H, H-1''a), 3.28 (d, *J* = 10.5 Hz, 1H, H-5), 3.17 (td, *J* = 12.5, 5.0 Hz, 1H, H-1''b), 3.06 (t, *J* = 11.8 Hz, 1H, H-1b), 2.98 (s, 2H, H_2-6''), 1.97 (t, *J* = 3.1 Hz, 3H, 3 x CH ada), 1.89 – 1.72 (m, 2H, H-2''), 1.81 –1.68 (m, 6H, CH_2 ada), 1.68 – 1.64 (m, 2H, H_2-4''), 1.58 (d, *J* = 2.9 Hz, 6H, 3 x CH_2 ada), 1.52 – 1.47 (m, 2H, H_2-3''). ^{13}C NMR (150 MHz, MeOD) δ 100.2 (C-1'), 83.3 (C-6''), 78.3 (C-3), 72.9 (C-5'), 72.3 (C-5''), 71.4 (C-2'), 70.9 (C-4), 70.1 (C-4'), 69.1 (C-3'), 68.1 (C-2), 66.2 (C-5), 62.6 (C-6), 60.4 (C-6'), 55.2 (C-1), 54.4 (C-1''), 41.0 (CH_2 ada), 38.4 (CH_2 ada), 35.2 (C_q ada), 30.3 (C-4''), 29.8 (CH ada), 24.7 (C-3''), 24.0 (C-2''). $[\alpha]^{20}_D$ = +31.5 (c = 0.2, MeOH). IR/cm^{-1}: 3385, 3161, 2374, 2349, 2320, 2063, 1683, 1558, 1506, 1436, 1207, 1138, 1082, 1039. HRMS: found 560.34239 $[C_{28}H_{49}NO_{10}+H]^+$, calculated for $[C_{28}H_{49}NO_{10}+H]^+$ 560.34292.

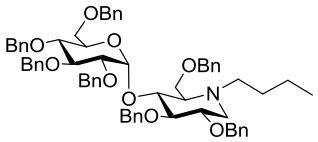
6-*O*-(α-D-Galactopyranosyl)-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxynojirimycin (17):

Melibio-DNJ (**1**, 32.5 mg, 0.1 mmol) was subjected to the general procedure B to generate **17** (13.0 mg, 27.0 mmol) in a yield of 27%. ^{1}H NMR (400 MHz, MeOD) δ 4.93 (d, *J* = 3.8 Hz, 1H, H-1'), 4.33 (d, *J* = 11.6 Hz, 1H, H-6'a), 3.93 – 3.87 (m, 2H, H-4, H-4'), 3.81 (t, *J* = 6.0 Hz, 1H, H-5'),



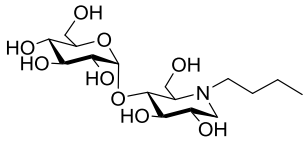
3.78 – 3.68 (m, 3H, H-2', H_2-6), 3.69 – 3.59 (m, 2H, H-2, H-3'), 3.55 (dd, *J* = 12.0, 4.7 Hz, 1H, H-1a), 3.45 (t, *J* = 6.2 Hz, 2H, H_2-5"), 3.40 – 3.32 (m, 2H, H-3, H-1"a), 3.26 (d, *J* = 9.7 Hz, 1H, H-5), 3.15 (td, *J* = 12.5, 5.1 Hz, 1H, H-1"b), 3.08 (s, 2H, H_2-6''), 3.04 (t, *J* = 11.8 Hz, 1H, H-1b), 1.88 – 1.71 (m, 2H, H_2-2"), 1.71 – 1.62 (m, 2H, H_2-4"), 1.50 – 1.43 (m, 2H, H_2-3"), 0.91 (s, 9H, H_3-8'', H_3-9'', H_3-10''). ^{13}C NMR (100 MHz, MeOD) δ 100.0 (C-1'), 82.6 (C-6''), 78.2 (C-3), 72.8 (C-5'), 72.1 (C-5"), 71.3 (C-2'), 70.8 (C-4), 70.0 (C-4'), 69.0 (C-3'), 68.0 (C-2), 66.2 (C-5), 62.5 (C-6), 60.3 (C-6'), 55.1 (C-1), 54.4 (C-1"), 32.9 (C-7''), 30.2 (C-4"), 27.1 (C_3-8'', C_3-9'', C_3-10''), 24.5 (C-3"), 24.0 (C-2"). $[\alpha]^{20}_D$ = +43.8 (c = 0.26, MeOH). IR/cm^{-1}: 3329, 2951, 2864, 1372, 1427, 1358, 1202, 1134, 1080, 1040. HRMS: found 482.29552 $[C_{22}H_{43}NO_{10}+H]^+$, calculated for $[C_{22}H_{43}NO_{10}+H]^+$ 482.29597.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-*N*-butyl-1-deoxynojirimycin (18):



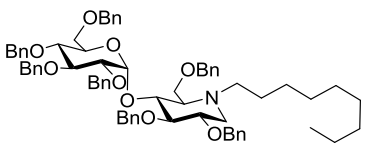
Protected *Malto*-DNJ (0.19 g, 0.2 mmol) was subjected to the general procedure C to generate **18** (0.12 g, 0.12 mmol) in a yield of 66%. R_F = 0.40 (4:1, PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.09 (m, 35H, H_{Ar} Bn), 5.74 (d, *J* = 3.4 Hz, 1H, H-1), 5.00 – 4.26 (m, 14H, 7 x CH_2 Bn), 4.10 (t, *J* = 8.2 Hz, 1H, H-4), 3.98 (t, *J* = 9.3 Hz, 1H, H-3'), 3.80 (t, *J* = 9.6 Hz, 1H, H-5'), 3.76 – 3.58 (m, 5H, H-2, H-3, H-4', H-6a, H-6'a), 3.55 – 3.50 (m, 3H, H-2', H-6b, H-6'b), 3.08 (dd, *J* = 11.1, 4.7 Hz, 1H, H-1a), 2.57 – 2.50 (m, 3H, H_2-1", H-5), 2.33 (t, *J* = 10.7 Hz, 1H, H-1b), 1.30 (m, 2H, H_2-2"), 1.15 – 1.05 (m, 2H, H_2-3"), 0.82 (t, *J* = 7.3 Hz, 3H, H_3-4"). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 – 137.8 (7 x C_q Bn), 128.4 – 126.8 (CH_{Ar} Bn), 95.9 (C-1'), 86.3 (C-3), 82.2 (C-3'), 79.7 (C-2'), 78.6 (C-2), 77.7 (C-4'), 75.6 – 72.4 (7 x CH_2 Bn), 72.3 (C-4), 70.9 (C-5'), 68.2 (C-6), 65.9 (C-6'), 63.1 (C-5), 53.4 (C-1), 52.4 (C-1"), 26.4 (C-2"), 20.6 (C-3"), 14.1 (C-4"). $[\alpha]^{20}_D$ = +15.6 (c = 1.0, $CHCl_3$). IR/cm^{-1}: 3063, 3030, 2922, 2964, 1497, 1453, 1363, 1092, 1073, 1028. HRMS: found 1012.53472 $[C_{65}H_{74}NO_9+H]^+$, calculated for $[C_{65}H_{74}NO_9+H]^+$ 1012.53581.

4-*O*-(α-D-Glucopyranosyl)-*N*-butyl-1-deoxynojirimycin (19):



Malto-DNJ (**18**, 0.19 g, 0.2 mmol) was subjected to the general procedure C to generate **19** (26.1 mg, 0.07 mmol) as a white solid in 58% yield. ^{1}H-NMR (400 MHz, MeOD) δ 5.13 (d, *J* = 3.8 Hz, 1H, H-1'), 3.92 (dd, *J* = 12.2, 2.4 Hz, 1H, H-6a), 3.88 (dd, *J* = 12.2, 2.1 Hz, 1H, H-6b), 3.84 (dd, *J* = 11.6, 2.1 Hz, 1H, H-6a'), 3.74 (ddd, *J* = 9.8, 5.9, 2.0 Hz, 1H, H-5'), 3.66 (dd, *J* = 11.6, 6.0 Hz, 1H, H-6b'), 3.63 (t, *J* = 9.3 Hz, 1H, H-3'), 3.52 (t, *J* = 9.2 Hz, 1H, H-4), 3.51 (dd, *J* = 9.8, 4.9 Hz, 1H, H-2), 3.47 (dd, *J* = 9.7, 3.8 Hz, 1H, H-2'), 3.37 (t, *J* =9.1 Hz, 1H, H-3), 3.27 (dd, *J* = 9.9, 9.0 Hz, 1H, H-4'), 2.97 (dd, *J* = 11.0, 4.7 Hz, 1H, H-1a), 2.79 (m, 1H, H-1''a), 2.63 (m, 1H, H-1''b), 2.20 (dd, *J* = 11.3, 1.7 Hz, 1H, H-5), 2.19 (m, 1H, H-1b), 1.49 – 1.42 (m, 2H, H_2-2''), 1.35 – 1.29 (m, 2H, H_2-3''), 0.95 (t, *J* = 7.3 Hz, 3H, H_3-4''). ^{13}C NMR (100 MHz, MeOD) δ 103.5 (C-1'), 84.0 (C-2), 80.4 (C-3), 75.1 (C-3'), 74.8 (C-5'), 74.3 (C-2'), 71.6 (C-4'), 70.2 (C-4), 66.1 (C-5), 62.8 (C-6'), 58.5 (C-6), 57.5 (C-1), 53.4 (C-1"), 27.3 (C-2"), 21.8 (C-3"), 14.4 (C-4"). $[\alpha]^{20}_D$ = +42.1 (c = 0.76, MeOH). IR/cm^{-1}: 3309, 2961, 2932, 2479, 1636, 1456, 1373, 1146, 1076, 1034. HRMS: found 382.20730 $[C_{16}H_{31}NO_9+H]^+$, calculated for $[C_{16}H_{31}NO_9+H]^+$ 382.20716.

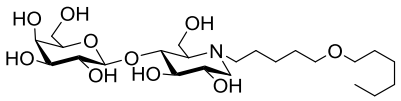
2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucosepyranosyl)-*N*-nonyl-1-deoxynojirimycin (20).



Protected *malto*-DNJ (0.19 g, 0.2 mmol) was subjected to the general procedure C to generate **20** (0.13 g, 0.12 mmol) in a yield of 66% (0.133 g, 0.123 mmol). R_F = 0.66 (4:1,

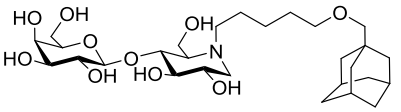
PE:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.10 (m, 35H, H_{Ar} Bn), 5.75 (d, *J* = 3.3 Hz, 1H, H-1), 5.01 – 4.26 (m, 14H, 7 x CH_2 Bn), 4.11 (t, *J* = 8.2 Hz, 1H, H-4), 3.99 (t, *J* = 9.2 Hz, 1H, H-3'), 3.80 (t, *J* = 9.2 Hz, 1H, H-5'), 3.76 – 3.58 (m, 5H, H-2, H-3, H-4', H-6a, H-6'a), 3.55 – 3.50 (m, 3H, H-2', H-6b, H-6'b), 3.08 (dd, *J* = 11.1, 4.7 Hz, 1H, H-1a), 2.57 – 2.50 (m, 3H, H_2-1'', H-5), 2.33 (t, *J* = 10.7 Hz, 1H, H-1b), 1.47-1.13 (m, 12H, H_2-2'' – H_2-7''), 1.12 – 1.02 (m, 2H, H_2-8''), 0.88 (t, *J* = 8.1, Hz, 3H, H_3-9''). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 – 137.8 (C_q Bn), 128.4 – 126.8 (CH_{Ar} Bn), 95.8 (C-1'), 86.3 (C-3), 82.1 (C-3'), 79.7 (C-2'), 78.6 (C-2), 77.7 (C-4'), 75.6 – 72.4 (7 x CH_2 Bn), 72.1 (C-4), 70 .9 (C-5'), 68.2 (C-6), 65.8 (C-6'), 63.0 (C-5), 53.4 (C-1), 32.0, 30.0, 29.6, 29.6, 29.3, 29.2, 27.4, 24.1, 22.8 (C-2'' – C-8''), 14.2 (C-9''). $[\alpha]^{20}_D$ = +16.0 (c = 1.02, $CHCl_3$). IR/cm^{-1}: 2954, 2925, 2853, 1539, 1506, 1093, 1073, 1028.

4-*O*-(β-D-Galactopyranosyl)-*N*-[5-(hexyloxy)pentyl]-1-deoxynojirimycin (21):



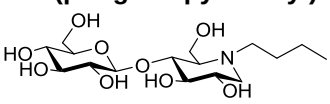
Lacto-DNJ was subjected to the general procedure A to generate **21** (5.6 mg, 0.01 mmol) in a yield of 11%. ^{1}H NMR (600 MHz, MeOD) δ 4.54 (d, *J* = 7.7 Hz, 1H, H-1'), 4.42 (d, *J* = 13.0 Hz, 1H, H-6a), 3.99 (d, *J* = 13.0 Hz, 1H, H-6b), 3.92 (dd, *J* = 3.3, 1.0 Hz, 1H, H-4'), 3.92 – 3.87 (m, 1H, H-4), 3.88 (dd, *J* = 11.5, 7.7 Hz, 1H, H-6'a), 3.86 – 3.83 (m, 1H, H-3), 3.81 (dd, *J* = 11.4, 4.4 Hz, 1H, H-6'b), 3.70 (q, *J* = 7.0 Hz, 1H, H-5'), 3.68 (dd, *J* = 12.3, 7.7 Hz, 1H, H-2'), 3.64 (t, *J* = 9.2 Hz, 1H, H-2), 3.59 (dd, *J* = 9.7, 3.3 Hz, 1H, H-3'), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5''), 3.55 – 3.51 (m, 1H, H-1a), 3.52 (t, *J* = 6.6 Hz, 2H, H_2-6''), 3.49 – 3.45 (m, 1H, H-1''a). 3.36 (d, *J* = 10.0 Hz, 1H, H-5), 3.33 – 3.26 (m, 1H, H-1''b), 3.13 (t, *J* = 11.7 Hz, 1H, H-1b), 1.95 – 1.80 (m, 2H, H_2-2''), 1.76 – 1.72 (m, 2H, H_2-4''), 1.68 – 1.62 (m, 2H, H_2-7''), 1.62 – 1.52 (m, 2H, H_2-3''), 1.49 – 1.36 (m, 6H, H_2-8'', H_2-9'', H_2-10''), 1.00 (t, *J* = 6.9 Hz, 3H, H_3-11''). ^{13}C NMR (150 MHz, MeOD) δ 106.1 (C-1'), 78.8 (C-4), 78.2 (C-5), 77.3 (C-2), 75.7 (C-3'), 73.4 (C-2'), 72.9 (C-6''), 72.2 (C-5''), 71.1 (C-4'), 68.4 (C-3), 67.1 (C-5), 63.4 (C-6'), 55.3 (C-1), 55.1 (C-1''), 55.1 (C-6), 33.7 (C-9''), 31.6 (C-7''), 31.0 (C-4''), 27.8 (C-8''), 25.3 (C-3''), 24.8 (C-2''), 24.5 (C-10''), 15.3 (C-11''). $[\alpha]^{20}_D$ = -4.0 (c = 0.2, MeOH). IR/cm^{-1}: 3395, 2956, 2872, 1670, 1435, 1201, 1142, 1080, 1047. HRMS: found 496.31127 $[C_{23}H_{45}NO_{10}+H]^+$, calculated for $[C_{23}H_{45}NO_{10}+H]^+$ 496.31162.

4-(β-D-Galactopyranosyl)-*N*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (22):



Lacto-DNJ (**3**) was subjected to the general procedure A to generate **22** (6.72 mg, 0.01 mmol) in a yield of 12%. ^{1}H NMR (400 MHz, MeOD) δ 4.54 (d, *J* = 7.7 Hz, 1H, H-1'), 4.42 (d, *J* = 12.9 Hz, 1H, H-6a), 3.99 (d, *J* = 12.3 Hz, 1H, H-6b), 3.91 (dd, *J* = 3.3, 1.1 Hz, 1H, H-4'), 3.90 – 3.82 (m, 2H, H-4, H-3), 3.88 (dd, *J* = 11.4, 7.7 Hz, 1H, H-6'a), 3.80 (dd, *J* = 11.5, 4.4 Hz, 1H, H-6'b), 3.69 (ddd, *J* = 7.6, 4.3, 1.1 Hz, 1H, H-5'), 3.67 (dd, *J* = 8.3, 7.6 Hz, 1H, H-2'), 3.64 – 3.59 (m, 1H, H-2), 3.58 (dd, *J* = 9.8, 3.3 Hz, 1H, H-3'), 3.57 – 3.51 (m, 1H, H-1a), 3.51 (t, *J* = 6.1 Hz, 2H, H-5''), 3.49 – 3.45 (m, 1H, H-1''a), 3.37 – 3.26 (m, 2H, H-5, H-1''b), 3.13 (t, *J* = 11.7 Hz, 1H, H-1b), 3.07 (s, 2H, H_2-6''), 2.06 – 2.02 (m, 3H, 3 x CH ada), 1.96 – 1.69 (m, 10H, H_2-4'', 3 x CH_2 ada), 1.68 – 1.63 (m, 6H, 3 x CH_2 ada), 1.63 – 1.51 (m, 2H, H_2-3''). ^{13}C NMR (100 MHz, MeOD) δ 105.8 (C-1'), 84.0 (C-6''), 78.8 (C-4'), 78.2 (C-5'), 76.9 (C-2), 75.7 (C-3'), 73.4 (C-2'), 72.9 (C-5''), 71.1 (C-4), 68.4 (C-3), 67.1 (C-5), 63.4 (C-6'), 54.8 (C-6), 54.9 (C-1), 54.9 (C-1''), 41.7 (CH_2-ada), 39.2 (CH_2-ada), 36.0 (C_q-ada), 31.0 (C-2''), 30.6 (CH-ada), 27.3 (C-3''), 25.4 (C-4''). $[\alpha]^{20}_D$ = -17.0 (c = 0.2, MeOH). IR/cm^{-1}: 3391, 2903, 2849, 1674, 1435, 1204, 1136, 1082, 1053. HRMS: found 560.34253 $[C_{28}H_{49}NO_{10}+H]^+$, calculated for $[C_{28}H_{49}NO_{10}+H]^+$ 560.34292.

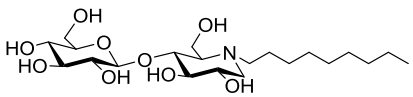
4-*O*-(β-D-glucopyranosyl)-*N*-butyl-1-deoxynojirimycin (23):



Cellibio-DNJ (**4**) was subjected to the general procedure A to generate **23** (6.5 mg, 0.02 mmol) in a yield of 17%. ^{1}H NMR (400

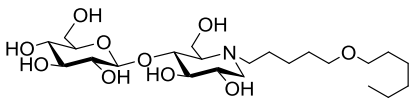
MHz, MeOD) δ 4.59 (d, *J* = 7.8 Hz, 1H, H-1'), 4.37 (dd, *J* = 12.9, 1.7 Hz, 1H, H-6a), 4.00 (dd, *J* = 12.9, 2.8 Hz, 1H, H-6b), 3.99 (dd, *J* = 11.8, 2.1 Hz, 1H, H-6'a), 3.87 (dd, *J* = 10.0, 9.0 Hz, 1H, H-4), 3.83 (ddd, *J* = 11.0, 9.1, 4.9 Hz, 1H, H-2), 3.75 (dd, *J* = 11.8, 6.0 Hz, 1H, H-6'b), 3.61 (t, *J* = 9.0 Hz, 1H, H-3), 3.53 – 3.33 (m, 6H, H-1a, H-1''a, H-2', H-3', H-4', H-5'), 3.30 – 3.18 (m, 2H, H-5, H-1''b), 3.03 (t, *J* = 11.5 Hz, 1H, H-1b), 1.87 – 1.71 (m, 2H, H_2-2''), 1.57 – 1.45 (m, 2H, H_2-3''), 1.10 (t, *J* = 7.4 Hz, 3H, H_3-4''). ^{13}C NMR (100 MHz, MeOD) δ 105.6 (C-1'), 79.6 (C-4), 79.2 (C-3'), 78.7 (C-5'), 77.4 (C-3), 75.8 (C-2'), 72.2 (C-4'), 68.8 (C-2), 67.1 (C-5), 63.3 (C-6'), 55.8 (C-6), 55.5 (C-1), 54.7 (C-1''), 27.2 (C-2''), 21.9 (C-3''), 14.8 (C-4''). $[\alpha]^{20}_D$ = -17.0 (c = 0.2, MeOH). HRMS: found 382.20752 $[C_{16}H_{31}NO_9+H]^+$, calculated for $[C_{16}H_{31}NO_9+H]^+$ 382.20716.

4-*O*-(β-D-Glucopyranosyl)-*N*-nonyl-1-deoxynojirimycin (24):



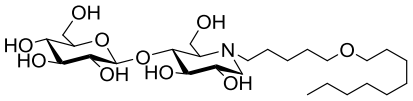
Cellobio-DNJ (**4**) was subjected to the general procedure A to generate **24** (3.6 mg, 0.01 mmol) in a yield of 8%. ^{1}H NMR (600 MHz, MeOD) δ 4.51 (d, *J* = 7.8 Hz, 1H, H-1'), 4.36 (d, *J* = 12.9 Hz, 1H, H-6a), 3.92 (dd, *J* = 11.8, 2.2 Hz, 1H, H-6'a), 3.90 (dd, *J* = 12.6, 2.4 Hz, 1H, H-6b), 3.81 (t, *J* = 9.7 Hz, 1H, H-4), 3.76 (td, *J* = 11.3, 5.3 Hz, 1H, H-2), 3.68 (dd, *J* = 11.8, 6.2 Hz, 1H, H-6'b), 3.55 (t, *J* = 9.1 Hz, 1H, H-3), 3.47 (dd, *J* = 12.2, 5.0 Hz, 1H, H-1a), 3.42 – 3.26 (m, 6H, H-1''a, H-2', H-3', H-4', H-5', H-5), 3.25 – 3.18 (m, 1H, H-1''b), 3.05 (t, *J* = 11.7 Hz, 1H, H-1b), 1.84 – 1.69 (m, 2H, H_2-2''), 1.50 – 1.26 (m, 12H, H_2-3'' – H_2-8''), 0.93 (t, *J* = 7.0, 3H, H_3-9''). ^{13}C NMR (150 MHz, MeOD) δ 104.4 (C-1'), 78.0 (C-5'), 77.8 (C-4), 77.5 (C-3'), 75.9 (C-3), 74.5 (C-2'), 70.9 (C-4'), 67.2 (C-2), 65.8 (C-5), 62.0 (C-6'), 53.9 (C-1''), 53.9 (C-1), 53.7 (C-6), 32.6, 30.1, 29.9, 29.8, 27.2, 23.7, 23.3 (C-2'' – C-8''), 14.0 (C-9''). $[\alpha]^{20}_D$ = +9.0 (c = 0.2, MeOH). IR/cm^{-1}: 3337, 2923, 1669, 1203, 1135, 1073. HRMS: found 452.28500 $[C_{21}H_{41}NO_9+H]^+$, calculated for $[C_{21}H_{41}NO_9+H]^+$ 452.28541.

4-*O*-(β-D-Glucopyranosyl)-*N*-[5-(hexyloxy)pentyl]-1-deoxynojirimycin (25):



Cellobio-DNJ (**4**) was subjected to the general procedure A to generate **25** (5.5 mg, 0.01 mmol) in a yield of 11%. ^{1}H NMR (600 MHz, MeOD) δ 4.58 (d, *J* = 7.8 Hz, 1H, H-1'), 4.42 (d, *J* = 13.0 Hz, 1H, H-6a), 3.99 (dd, *J* = 11.8, 2.2 Hz, 1H, H-6'a), 3.98 (d, *J* = 12.1 Hz, 1H, H-6b), 3.87 (t, *J* = 9.7 Hz, 1H, H-4), 3.83 (ddd, *J* = 11.1, 10.6, 4.9 Hz, 1H, H-2), 3.75 (dd, *J* = 11.9, 6.2 Hz, 1H, H-6'b), 3.55 (t, *J* = 6.3 Hz, 2H, H_2-6''), 3.55 – 3.51 (m, 1H, H-1a), 3.52 (t, *J* = 6.6 Hz, 2H, H_2-5''), 3.49 – 3.44 (m, 1H, H-1''a), 3.46 (t, *J* = 9.0 Hz, 1H, H-3'), 3.45 (ddd, *J* = 9.1, 6.2, 2.3 Hz, 1H, H-5'), 3.39 (t, *J* = 9.4 Hz, 1H, H-4'), 3.36 (dd, *J* = 9.1, 7.9 Hz, 1H, H-2'), 3.35 – 3.26 (m, 2H, H-5, H-1''b), 3.11 (t, *J* = 11.4 Hz, 1H, H-1b), 1.94 – 1.77 (m, 2H, H_2-2''), 1.78 – 1.71 (m, 2H, H_2-4''), 1.67 – 1.63 (m, 2H, H_2-7''), 1.60 – 1.53 (m, 2H, H_2-3''), 1.48 – 1.34 (m, 6H, H_2-8'', H_2-9'', H_2-10''), 1.00 (t, *J* = 6.9 Hz, 3H, H_3-11''). ^{13}C NMR (150 MHz, MeOD) δ 105.6 (C-1'), 79.2 (C-5'), 78.8 (C-4, C-3'), 77.2 (C-3), 75.8 (C-2'), 73.0 (C-5''), 72.2 (C-6''), 72.1(C-4'), 68.5(C-2), 67.1 (C-5), 63.3 (C-6'), 55.3 (C-1), 55.0 (C-1'), 55.0 (C-6), 33.7 (C-9''), 31.6 (C-7''), 31.0 (C-4''), 27.8 (C-8''), 25.4 (C-3''), 24.8 (C-2''), 24.6 (C-10''), 15.3 (C-11''). $[\alpha]^{20}_D$ = +0.3 (c = 1.0, MeOH). IR/cm^{-1}: 3298, 2874, 2511, 1635, 1456, 1317, 1015. HRMS: found 496.31124 $[C_{23}H_{45}NO_{10}+H]^+$, calculated for $[C_{23}H_{45}NO_{10}+H]^+$ 496.31162.

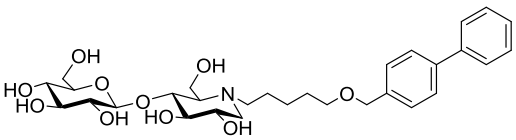
4-*O*-(β-D-Glucopyranosyl)-*N*-[5-(nonyloxy)pentyl]-1-deoxynojirimycin (26):



Cellobio-DNJ (**4**) was subjected to the general procedure A to generate **26** (4.8 mg, 0.01 mmol) in a yield of 9%. ^{1}H NMR (600 MHz, MeOD) δ 4.51 (d, *J* = 7.8 Hz, 1H, H-1'), 4.34 (d, *J* = 12.6 Hz, 1H, H-6a), 3.92 (dd, *J* = 11.8, 2.3 Hz, 1H, H-6'a), 3.84 – 3.73 (m, 2H, H-4, H-2), 3.68 (dd, *J* = 11.8, 6.2 Hz, 1H, H-6'b), 3.54 (t, *J* = 8.9 Hz, 1H, H-3), 3.48 (t, *J* = 6.3 Hz, 2H, H_2-5''), 3.45 (t, *J* = 6.6 Hz, 2H, H_2-6''), 3.49 – 3.45 (m, 1H, H-1a), 3.40 – 3.18 (m, 7H, H-1''a, H-1''b, H-2', H-3', H-4', H-5', H-5), 1.85 – 1.73 (m, 2H, H_2-2''), 1.71 – 1.63 (m, 2H, H_2-4''), 1.61 – 1.55 (m, 2H, H_2-7''), 1.54 – 1.44 (m, 2H, H_2-3''), 1.42 – 1.26 (m, 12H,

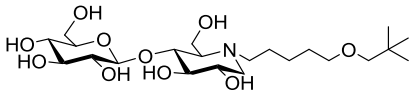
H_2-8'' – H_2-13''), 0.92 (t, *J* = 7.0 Hz, 3H, H_3-14''). ^{13}C NMR (150 MHz, MeOD) δ 103.4 (C-1'), 77.0 (C-4), 76.8 (C-5'), 76.5 (C-3'), 75.2 (C-3), 73.5 (C-2'), 70.7 (C-6''), 70.0 (C-5''), 69.9 (C-4'), 61.0 (C-2), 53.1 (C-6'), 52.9 (C-1), 52.7 (C-6), 48.0 (C-1''), 31.6, 29.4, 29.3, 29.2, 29.0, 28.8, 25.9, 23.1, 22.5, 22.3, 13.0 (C-2'' – 4'', C-7'' – C-14''). $[\alpha]^{20}_D$ = -7.0 (c = 0.1, MeOH). IR/cm^{-1}: 3383, 2933, 1705, 1203, 1142. HRMS: found 538.35812 $[C_{26}H_{51}NO_{10}+H]^+$, calculated for $[C_{26}H_{51}NO_{10}+H]^+$ 538.35857.

4-*O*-(β-D-Glucopyranosyl)-*N*-[(biphenyl-4-yl-methoxy)-pentyl]-1-deoxynojirimycin (27):



Cellobio-DNJ (**4**) was subjected to the general procedure A and generated **27** (8.7 mg, 0.02 mmol) in a yield of 15%. ^{1}H NMR (600 MHz, MeOD) δ 7.66 – 7.29 (m, 9H, H_{Ar} BiPh), 4.57 (s, 2H, H_2-6''), 4.50 (d, *J* = 7.9 Hz, 1H, H-1'), 4.34 (d, *J* = 12.9 Hz, 1H, H-6a), 3.91 (dd, *J* = 11.8, 2.2 Hz, 1H, H-6'a), 3.90 (d, *J* = 13.5 Hz, 1H, H-6b), 3.82 – 3.73 (m, 2H, H-2, H-4), 3.68 (dd, *J* = 11.8, 6.2 Hz, 1H, H-6'b), 3.59 (t, *J* = 6.2 Hz, 2H, H_2-5''), 3.56 – 3.51 (m, 1H, H-3), 3.49 – 3.43 (m, 1H, H-1a), 3.43 – 3.16 (m, 7H, H-1''a, H-1''b, H-2', H-3', H-4', H-5', H-5), 3.02 (t, *J* = 11.7 Hz, 1H, H-1b), 1.86 – 1.77 (m, 2H, H_2-2''), 1.76 – 1.70 (m, 2H, H_2-3''), 1.60 – 1.48 (m, 2H, H_2-4''). ^{13}C NMR (150 MHz, MeOD) δ 141.7 – 127.6 (C_{Ar} BiPh), 104.3 (C-1'), 78.0 (C-4), 77.7 (C-5'), 77.5 (C-3'), 76.0 (C-3), 74.5 (C-2'), 73.3 (C-6''), 70.9 (C-4'), 70.5 (C-5''), 67.3 (C-2), 65.8 (C-5), 62.0 (C-6), 54.3 (C-1), 54.1 (C-6), 53.8 (C-1''), 29.7 (C-4''), 24.2 (C-3''), 23.5 (C-2''). $[\alpha]^{20}_D$ = +0.5 (c = 0.2, MeOH). IR/cm^{-1}: 3368, 2318, 1674, 1205, 1134, 1080. HRMS: found 578.29406 $[C_{30}H_{43}NO_{10}+H]^+$, calculated for $[C_{30}H_{43}NO_{10}+H]^+$ 578.29597.

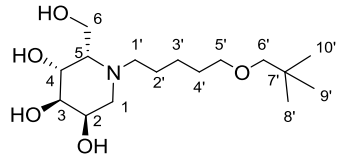
4-*O*-(β-D-Glucopyranosyl)-*N*-[5-(3,3-dimethyl-1-propyloxy)pentyl]-1-deoxynojirimycin (28):



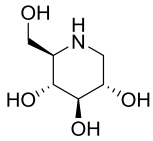
Cellobio-DNJ (**4**) was subjected to the general procedure A and generated **28** (4.8 mg, 0.01 mmol) in a yield of 10%. ^{1}H NMR (400 MHz, MeOD) δ 4.58 (d, *J* = 7.8 Hz, 1H, H-1'), 4.30 (dd, *J* = 12.4, 1.7 Hz, 1H, H-6'a), 3.98 (dd, *J* = 12.1, 4.5 Hz, 1H, H-6a), 3.98 (d, *J* = 12.0 Hz, 1H, H-6'b), 3.81 (t, *J* = 9.6 Hz, 1H, H-4), 3.81 – 3.73 (m, 1H, H-2), 3.75 (dd, *J* = 11.9, 6.0 Hz, 1H, H-6b), 3.53 (t, *J* = 9.6 Hz, 2H, H_2-5''), 3.50 – 3.45 (m, 2H, H-3, H-5'), 3.45 – 3.41 (m, 2H, H-4', H-2'), 3.35 (dd, *J* = 9.0, 7.8 Hz, 1H, H-1a), 3.29 – 3.19 (m, 1H, H-1''a), 3.17 (s, 2H, H_2-6''), 3.14 – 3.03 (m, 1H, H-1''b), 3.00 (d, *J* = 9.3 Hz, 1H, H-5), 2.81 (t, *J* = 11.5 Hz, 1H, H-1b), 1.86 – 1.68 (m, 4H, H_2-2'', H_2-3''), 1.63 – 1.48 (m, 2H, H_2-4''), 1.00 (s, 9H, H_3-8'', H_3-9'', H_3-10''). ^{13}C NMR (100 MHz, MeOD) δ 105.6 (C-1'), 83.4 (C-6''), 80.6 (C-4), 79.1 (C-5'), 78.8 (C-3), 78.0 (C-3'), 75.9 (C-2'), 73.0 (C-5''), 72.2 (C-4'), 69.6 (C-2), 67.1 (C-5), 63.3 (C-6), 56.2 (C-6'), 54.7 (C-1), 54.1 (C-1''), 33.8 (C-7''), 31.2 (C-2''), 28.0 (C-8'', 9'', 10''), 25.7 (C-4''), 25.3 (C-3''). $[\alpha]^{20}_D$ = +0.5 (c = 1.0, MeOH). IR/cm^{-1}: 3308, 2980, 2875, 2349, 1635, 1080, 1031. HRMS: found 482.29552 $[C_{22}H_{43}NO_{10}+H]^+$, calculated for $[C_{22}H_{43}NO_{10}+H]^+$ 482.29597.

Synthesis of *N*-Alkylated DNJ and DNJ congeners

***Figure 19**: Proton and carbon NMR numbering of iminosugars*

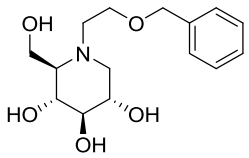


1-Deoxynojirimycin (85):



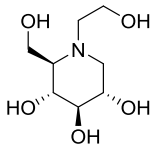
^{1}H NMR (400 MHz, MeOD) δ 3.92 (dd, *J* = 10.9, 3.1 Hz, 1H, H-6a), 3.67 (dd, *J* = 10.9, 6.5 Hz, 1H, H-6b), 3.49 (ddd, *J* = 10.6, 8.7, 5.1 Hz, 1H, H-2), 3.28 (t, *J* = 8.1 Hz, 1H, H-3), 3.24 (t, *J* = 9.1 Hz, 1H, H-4), 3.18 (dd, *J* = 12.1, 5.1 Hz, 1H, H-1a), 2.54 (ddd, *J* = 9.4, 6.4, 3.1 Hz, 1H, H-5), 2.52 (dd, *J* = 12.1, 10.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 81.5 (C-3), 74.2 (C-4), 73.5 (C-2), 64.0 (C-6), 63.7 (C-5), 51.9 (C-1).

***N*-Benzyloxyethyl-1-deoxynojirimycin (90):**



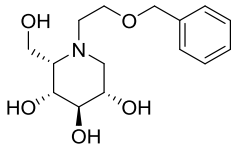
DNJ (**85**) was subjected to the general procedure A and generated **90** (12.4 mg, 0.04 mmol) in a yield of 38%. ^{1}H NMR (400 MHz, MeOD) δ 7.45 – 7.33 (m, 5H, H_{Ar} Bn), 4.61 (s, 2H, CH_2 Bn), 4.02 (dd, *J* = 12.1, 2.7 Hz, 1H, H-6a), 3.92 (dd, *J* = 12.1, 2.8 Hz, 1H, H-6b), 3.73 – 3.69 (m, 2H, H_2-2'), 3.55 (ddd, *J* = 10.5, 9.1, 4.8 Hz, 1H, H-2), 3.45 (t, *J* = 9.3 Hz, 1H, H-4), 3.23 (t, *J* = 9.1 Hz, 1H, H-3), 3.19 – 3.13 (m, 1H, H-1'a), 3.15 (dd, *J* = 10.5, 5.1 Hz, 1H, H-1a), 2.84 (dt, *J* = 14.5, 4.6 Hz, 1H, H-1'b), 2.38 (dd, *J* = 11.3, 10.5 Hz, 1H, H-1b), 2.30 (dt, *J* = 9.5, 2.7 Hz, 1H, H-5). ^{13}C NMR (100 MHz, MeOD) δ 131.3 – 129.6 (C_{Ar}), 81.3 (C-3), 75.0 (CH_2 Bn), 72.6 (C-4), 71.5 (C-2), 69.4 (C-2'), 68.5 (C-5), 60.2 (C-6), 59.3 (C-1), 53.4 (C-1'). HRMS: found 298.16505 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

***N*-Hydroxyethyl-1-deoxynojirimycin (90a):**



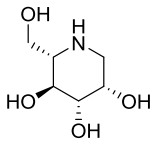
90 (60 mg, 0.2 mmol) was dissolved in 5 mL ethanol and the pH of the solvent was adjusted to 2 with aqueous HCl (1M). After the solution was flushed with argon (3 x), a catalytic amount of Pd/C (10%) was added. The reaction mixture was exposed to H_2 atmosphere (3 bar) for 18 hours. TLC analysis showed completely consumption of **90.** The reaction mixture was filtered over a pad of Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% → 20% methanol in DCM + 1% NH_4OH) to give **90a** as a colorless oil in a of yield 65% (27 mg, 0.13 mmol). ^{1}H NMR (400 MHz, MeOD) δ 4.21 (dd, *J* = 12.6, 0.9 Hz, 1H, H-6a), 4.08 (dd, *J* = 12.6, 2.9 Hz, 1H, H-6b), 4.05 (t, *J* = 5.1 Hz, 2H, H_2-2'), 3.82 (ddd, *J* = 11.2, 9.3, 4.9 Hz, 1H, H-2), 3.74 (dd, *J* = 12.1, 4.9 Hz, 1H, H-1a), 3.71 (dd, *J* = 10.4, 9.2 Hz, 1H, H-4), 3.70 – 3.63 (m, 1H, H-1'a), 3.47 (t, *J* = 9.2 Hz, 1H, H-3), 3.46 – 3.41 (m, 1H, H-1'a), 3.26 (d, *J* = 10.9 Hz, 1H, H-5), 3.20 (t, *J* = 11.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 79.0 (C-3), 69.7 (C-4), 69.3 (C-5), 68.6 (C-2), 57.7 (C-2'), 57.0 (C-1'), 56.5 (C-1), 56.0 (C-6). $[\alpha]^{20}_D$ = -42.0 (c = 0.2, MeOH). HRMS: found 208.11795 $[C_8H_{17}NO_5+H]^+$, calculated for $[C_8H_{17}NO_5+H]^+$ 208.11795.

***N*-Benzyloxyethyl-L-*ido*-1-deoxynojimycin (97):**



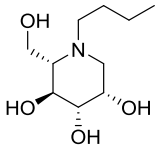
L-*ido*-DNJ was subjected to the general procedure A and generated **97** (21 mg, 0.07 mmol) in a yield of 12%. ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.29 (m, 5H, H_{Ar} Bn), 4.62 (s, 2H, CH_2 Bn), 4.03 (d, *J* =11.2, 6.4 Hz, 1H, H-6a), 3.87 (dd, *J* = 10.8, 6.4 Hz, 1H, H-6b), 3.80 (dd, *J* = 8.9, 5.3 Hz, 1H, H-4), 3.70 (t, *J* = 5.6 Hz, 2H, H_2-2'), 3.63 (ddd, *J* = 12.7, 8.9, 5.1 Hz, 1H, H-2), 3.45 (t, *J* = 8.5 Hz, 1H, H-3), 3.17 (m, *J* = 5.6 Hz, 1H, H-5), 3.11 (t, *J* = 5.6 Hz, 1H, H-1'a), 3.04 (t, *J* = 5.6 Hz, 1H, H-1'b), 2.97 (dd, *J* = 12.7, 4.9 Hz, 1H, H-1a), 2.75 (dd, *J* = 12.6, 9.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 140.5 – 129.0 (CH_{Ar} Bn), 76.7 (C-3), 75.0 (CH_2 Bn), 73.3 (C-4), 71.9 (C-2), 70.7 (C-2'), 65.7 (C-5), 58.8 (C-6), 56.2 (C-1'), 53.7 (C-1). $[\alpha]^{20}_D$ = -18.0 (c = 0.5, MeOH). IR/cm^{-1}: 3331, 2864, 1653, 1456, 1362, 1059, 1027. HRMS: found 298.16512 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

L-*Manno*-1-deoxynojimycin (129):



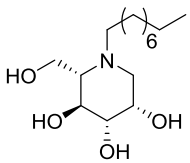
2,3,4-Tri-*O*-benzyl-L-*manno*-1-deoxynojimycin (0.84 g, 1.94 mmol) was dissolved in ethanol (100 mL) and pH of the solution was adjusted to 2 with aqueous HCl (1M). The solvent was flushed with argon (3 x), a catalytic amount of Pd/C (10%) was added, and the reaction mixture was exposed to H_2 atmosphere (2 bar) for 18 hours. After TLC analysis showed completely consumption of the starting compound, the reaction mixture was filtered over a pad of Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% → 20% methanol in DCM + 1% NH_4OH) to give **129** (0.19 g, 1.14 mmol) in a yield of 59%**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 1H, H-2), 4.02 (d, *J* = 12.0 Hz, 1H, H-6a), 3.86 (d, *J* = 12.4 Hz, 1H, H-6b), 3.84 (d, *J* = 10.8 Hz, 1H, H-4), 3.63 (d, *J* = 9.6 Hz, 1H, H-3), 3.36 (d, *J* = 13.2 Hz, 1H, H-1a), 3.25 (d, *J* = 13.6 Hz, 1H, H-1b), 3.12 – 3.07 (m, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.0 (C-3), 66.2 (C-4), 66.2 (C-2), 61.0 (C-5), 58.2 (C-6), 34.1 (C-1). $[\alpha]^{20}_D$ = +4.3 (c = 1.0, MeOH). IR/cm^{-1}: 3348, 2924, 1653, 1448, 1144, 1081, 1047. HRMS: found 164.09167 $[C_6H_{13}NO_4+H]^+$, calculated for $[C_6H_{13}NO_4+H]^+$ 164.09173.

***N*-Butyl- L-*manno*-1-deoxynojimycin (130):**



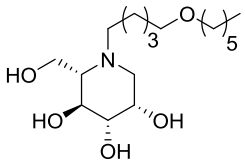
129 was subjected to the general procedure A and generated **130** (18 mg, 0.04 mmol) in a yield of 42%. ^{1}H NMR (400 MHz, MeOD) δ 4.21 (ddd, *J* = 3.9, 3.2, 1.5 Hz, H-2), 4.17 (dd, *J* = 12.7, 2.9 Hz, 1H, H-6a), 4.05 (dd, *J* = 12.9, 2.8 Hz, 1H, H-6b), 4.04 (t, *J* = 9.5 Hz, 1H, H-4), 3.66 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3), 3.55 (dd, *J* = 12.9, 3.7 Hz, 1H, H-1a), 3.47 (d, *J* = 13.0 Hz, 1H, H-1b), 3.44 – 3.35 (m, 2H, H_2-1'), 3.14 (dt, *J* = 9.9, 3.0 Hz, 1H, H-5), 1.94 – 1.72 (m, 2H, H_2-2'), 1.54 – 1.50 (m, 2H, H_2-3'), 1.10 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (100 MHz, MeOD) δ 75.0 (C-3), 68.6 (C-5), 68.0 (C-2), 67.8 (C-4), 56.9 (C-6), 56.9 (C-1), 55.2 (C-1'), 26.6 (C-2'), 21.8 (C-3'), 14.8 (C-4'). $[\alpha]^{20}_D$ = -7.2 (c = 1.0, MeOH). IR/cm^{-1}: 3244, 2954, 2872, 2619, 1635, 1435, 1259, 1076, 1020. HRMS: found 220.15434 $[C_{10}H_{21}NO_4+H]^+$, calculated for $[C_{10}H_{21}NO_4+H]^+$ 220.15433.

***N*-Nonyl- L-*manno*-1-deoxynojimycin (131):**



129 was subjected to the general procedure A and generated **131** (10 mg, 0.03 mmol) in a yield of 17%. ^{1}H NMR (400 MHz, MeOD) δ 4.00 (dd, *J* = 11.8, 2.6 Hz, 1H, H-6a), 3.96 – 3.92 (m, 1H, H-2), 3.95 (dd, *J* = 11.7, 2.9 Hz, 1H, H-6b), 3.78 (t, *J* = 9.1 Hz, 1H, H-4), 3.42 (dd, *J* = 9.0, 3.4 Hz, 1H, H-3), 3.11 (dd, *J* = 12.3, 3.9 Hz, 1H, H-1a), 2.95 – 2.83 (m, 1H, H-1'a), 2.80 – 2.70 (m, 1H, H-1'b), 2.66 (d, *J* = 12.3 Hz, 1H, H-1b), 2.32 – 2.28 (m, 1H, H-5), 1.65 – 1.51 (m, 2H, H_2-2'), 1.47 – 1.32 (m, 12H, H_2-3' – H_2-8'), 0.94 (t, *J* = 7.1 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 77.2 (C-3), 70.2 (C-4), 70.2 (C-2), 67.9 (C-5), 59.7 (C-6), 57.3 (C-1), 54.8 (C-1'), 33.9, 31.6, 31.5, 31.3, 29.4, 26.0, 24.6 (C-2' – C-8'), 15.3 (C-9'). $[\alpha]^{20}_D$ = +6.0 (c = 1.0, MeOH). IR/cm^{-1}: 3392, 2924, 2857, 2503, 1635, 1435, 1273, 1082. HRMS: found 290.23291 $[C_{15}H_{31}NO_4+H]^+$, calculated for $[C_{15}H_{31}NO_4+H]^+$ 290.23258.

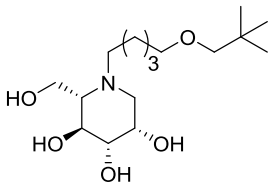
***N*-[5-(Hexyloxy)pentyl]- L-*manno*-1-deoxynojimycin (132)**



129 was subjected to the general procedure A and generated **132** (27 mg, 0.08 mmol) in a yield of 41%. ^{1}H NMR (400 MHz, MeOD) δ 3.92 (dd, *J* = 4.7, 2.7 Hz, 2H, H_2-6), 3.90 – 3.86 (m, 1H, H-2), 3.72 (t, *J* = 9.1 Hz, 1H, H-4), 3.36 (dd, *J* = 8.8, 3.1 Hz, 1H, H-3), 3.06 (dd, *J* = 12.4, 3.9 Hz, 1H, H-1a), 2.92 – 2.78 (m, 1H, H-1'a), 2.75 – 2.65 (m, 1H, H-1'b), 2.61 (d, *J* = 12.4 Hz, 1H, H-1b), 2.25 (d, *J* = 9.0 Hz, 1H, H-5), 1.74 – 1.27 (m, 14H, H_2-2', H_2-3', H_2-4', H_2-7', H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 7.1 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 77.2 (C-3), 72.8 (C-6'), 72.6 (C-5'), 70.2 (C-2), 70.2 (C-4), 67.9 (C-5), 59.7 (C-6), 57.2 (C-1), 54.7 (C-1'), 33.7, 31.6, 31.4, 27.8, 26.0, 25.8, 24.6 (C-2' – C-4', C-7' – C-10'), 15.3 (C-11').

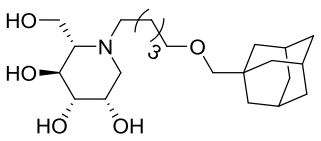
$[\alpha]^{20}_D$ = +31.5 (c = 1.0, MeOH). IR/cm^{-1}: 3392, 2932, 2867, 1684, 1456, 1373, 1099. HRMS: found 334.25936 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

_N_-[5-(3,3-Dimethyl-1-propyloxy)pentyl]- L-_manno_-1-deoxynojimycin (133):



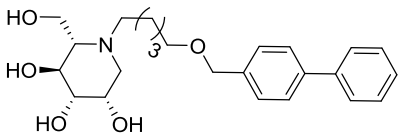
129 was subjected to the general procedure A and generated **133** (15 mg, 0.05 mmol) in a yield of 24%. ^{1}H NMR (400 MHz, MeOD) δ 4.00 (dd, *J* = 11.9, 2.8 Hz, 1H, H-6a), 3.96 (dd, *J* = 11.7, 2.9 Hz, 1H, H-6b), 3.95 – 3.92 (m, 1H, H-2), 3.78 (t, *J* = 9.1 Hz, 1H, H-4), 3.51 (t, *J* = 6.4 Hz, 2H, H-5'), 3.42 (dd, *J* = 8.5, 3.4 Hz, 1H, H-3), 3.16 (s, 2H, H_2-6'), 3.11 (dd, *J* = 12.4, 3.9 Hz, 1H, H-1a), 2.98 – 2.81 (m, 1H, H-1'a), 2.81 – 2.69 (m, 1H, H-1'b), 2.65 (d, *J* = 12.3 Hz, 1H, H-1b), 2.29 (d, *J* = 8.9 Hz, 1H, H-5), 1.73 – 1.66 (m, 2H, H_2-4'), 1.65 – 1.56 (m, 2H, H_2-2'), 1.51 – 1.37 (m, 2H, H_2-3'), 0.99 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (100 MHz, MeOD) δ 81.1 (C-6'), 75.0 (C-3), 71.0 (C-5'), 68.0 (C-2), 68.0 (C-4), 65.6 (C-5), 57.5 (C-6), 55.0 (C-1), 52.5 (C-1'), 31.5 (C-4'), 29.2 (C-7'), 25.7 (C-8',9',10'), 23.8 (C-3'), 23.5 (C-2'). $[\alpha]^{20}_D$ = +34.0 (c = 0.2, MeOH). IR/cm^{-1}: 3390, 2955, 2507, 1645, 1435, 1273, 1089. HRMS: found 320.24339 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

_N_-[5-(Adamantan-1-yl-methoxy)pentyl]- L-_manno_-1-deoxynojimycin (84):



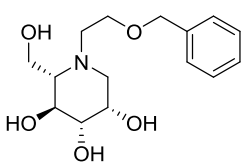
129 was subjected to the general procedure A and generated **84** (14 mg, 0.04 mmol) in a yield of 18%. ^{1}H NMR (600 MHz, MeOD) δ 4.22 – 4.19 (m, 1H, H-2), 4.16 (dd, *J* = 12.7, 3.3 Hz, 1H, H-6a), 4.05 (dd, *J* = 12.7, 2.9 Hz, 1H, H-6b), 4.02 (t, *J* = 9.3 Hz, 1H, H-4), 3.69 – 3.62 (m, 1H, H-3), 3.60 (t, *J* = 7.3 Hz, 2H, H_2-5'), 3.57 (s, 2H, H_2-6'), 3.53 (dd, *J* = 12.8, 4.0 Hz, 1H, H-1a), 3.47 – 3.41 (m, 3H, H_2-1', H-1b), 3.12 (br s, 1H, H-5), 2.07 – 1.98 (m, 3H, 3 x CH ada), 1.95 – 1.91 (m, 2H, H_2-2'), 1.87 – 1.80 (m, 3H, 3 x CH_2 ada), 1.80 – 1.70 (m, 7H, 3 x CH_2 ada, C-4'), 1.65 (d, *J* = 2.8 Hz, 6H, 3 x CH_2 ada), 1.46 (t, *J* = 7.4 Hz, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 75.1 (C-3), 71.7 (C-6'), 68.8 (C-5'), 68.6 (C-5), 68.0 (C-2), 68.0 (C-4), 56.7 (C-6), 56.6 (C-1), 55.0 (C-1'), 45.7 (C-3'), 44.7 (CH_2 ada), 39.0 (CH_2 ada), 33.6 (C_q ada), 31.0 (CH ada), 28.7 (C-2'). IR/cm^{-1}: 3393, 2901, 2830, 1684, 1506, 1456, 1418, 1396, 1373, 1078. $[\alpha]^{20}_D$ = +13.8 (c = 0.5, MeOH). HRMS: found 398.28949 $[C_{22}H_{39}NO_5+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.29010.

_N_-[(Biphenyl-4-yl-methoxy)pentyl]- L-_manno_-1-deoxynojimycin (134):



129 was subjected to the general procedure A and generated **134** (15 mg, 0.04 mmol) in a yield of 18%. ^{1}H NMR (400 MHz, MeOD) δ 7.66 – 7.30 (m, 9H, H_{Ar} BiPh), 4.45 (s, 2H, H_2-6'), 3.97 (dd, *J* = 11.7, 2.7 Hz, 1H, H-6a), 3.94 (dd, *J* = 11.7, 2.9 Hz, 1H, H-6b), 3.91 (dd, *J* = 3.7, 2.0 Hz, 1H, H-2), 3.75 (t, *J* = 9.1 Hz, 1H, H-4), 3.48 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.38 (d, *J* = 3.4 Hz, 1H, H-3), 3.05 (dd, *J* = 12.3, 3.9 Hz, 1H, H-1a), 2.84 (dt, *J* = 13.4, 8.5 Hz, 1H, H-1'a), 2.68 (dt, *J* = 13.4, 8.2 Hz, 1H, H-1'b), 2.57 (dd, *J* = 12.3, 1.8 Hz, 1H, H-1b), 2.22 (dt, *J* = 9.3, 2.7 Hz, 1H, H-5), 1.67 – 1.63 (m, 2H, H_2-4'), 1.57 – 1.54 (m, 2H, H_2-2'), 1.45 – 1.34 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 144.4 – 129.1 (C_{Ar} BiPh), 77.4 (C-3), 72.7 (C-6'), 72.3 (C-5'), 70.4 (C-2), 70.4 (C-4), 67.8 (C-5), 59.9 (C-6), 57.3 (C-1), 54.6 (C-1'), 31.4 (C-4'), 26.1 (C-3'), 25.9 (C-2'). $[\alpha]^{20}_D$ = +17.4 (c = 0.5, MeOH). IR/cm^{-1}: 3321, 2941, 2866, 2349, 2326, 1636, 1558, 1506, 1456, 1202, 1088, 744. HRMS: found 416.24303 $[C_{24}H_{33}NO_5+H]^+$, calculated for $[C_{24}H_{33}NO_5+H]^+$ 416.24315.

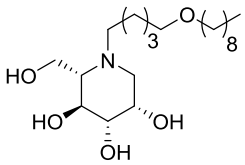
_N_-Benzyloxyethyl- L-_manno_-1-deoxynojimycin (135):



129 was subjected to the general procedure A and generated **135** (30 mg, 0.10 mmol) in a yield of 17%. ^{1}H NMR (400 MHz, MeOD) δ 7.58 – 7.28 (m, 5H, H_{Ar} Bn), 4.68 – 4.60 (m, 1H, H-2'a), 4.62 (s, 2H, CH_2 Bn),

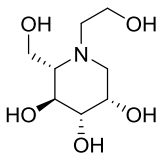
4.09 (dd, *J* = 12.7, 2.9 Hz, 1H, H-6a), 4.03 (dd, *J* = 12.7, 3.0 Hz, 1H, H-6b), 4.01 – 3.97 (m, 1H, H-2'b), 4.12 (dd, *J* = 3.8, 1.4 Hz, 1H, H-2), 3.94 (t, *J* = 9.2, 1H, H-4), 3.69 – 3.61 (m, 1H, 1H, H-1'a), 3.60 (dd, *J* = 9.1, 3.0 Hz, 1H, H-3), 3.34 – 3.29 (m, 1H, H-1'b), 3.18 (dd, *J* = 12.9, 4.0 Hz, H-1a), 3.09 (d, *J* = 9.6 Hz, 1H, H-5), 2.93 (d, *J* = 12.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 137.5 – 127.7 (C_{Ar} Bn), 72.9 (CH_2 Bn), 72.2 (C-3), 66.6 (C-5), 66.2 (C-4), 66.1 (C-2), 56.0 (C-2'), 55.0 (C-6), 53.2 (C-1), 52.1 (C-1'). $[\alpha]^{20}_D$ = +8.8 (c = 1.0, MeOH). IR/cm^{-1}: 3381, 2913, 1653, 1212, 1101, 1079, 1027. HRMS: found 298.16505 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

N-[5-(Nonyloxy)pentyl]- L-*manno*-1-deoxynojimycin (136):



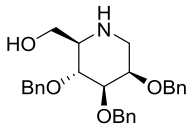
129 was subjected to the general procedure A and generated **136** (22 mg, 0.06 mmol) in a yield 29%. ^{1}H NMR (400 MHz, MeOD) δ 4.16 (s, 1H, H-2), 4.11 (dd, *J* = 12.8, 2.8 Hz, 1H, H-6a), 3.99 (dd, *J* = 12.6, 2.7 Hz, 1H, H-6b), 3.97 (t, *J* = 9.5 Hz, 1H, H-4), 3.61 (dd, *J* = 9.3, 3.0 Hz, 1H, H-3), 3.51 – 3.36 (m, 2H, H_2-1), 3.35 – 3.31 (m, 2H, H_2-1'), 3.48 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.46 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.13 – 3.06 (m, 1H, H-5), 1.89 – 1.73 (m, 2H, H_2-2'), 1.70 – 1.66 (m, 2H, H_2-4'), 1.61 – 1.58 (m, 2H, H_2-7'), 1.52 – 1.48 (m, 2H, H_2-3'), 1.43 – 1.27 (m, 12H, H_2-8' – H_2-13'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 75.0 (C-3), 72.9 (C-6'), 72.2 (C-5'), 68.6 (C-5), 68.0 (C-2), 67.8 (C-4), 56.9 (C-1), 56.9 (C-6), 55.3 (C-1'), 33.9, 31.6, 31.6, 31.5, 31.3, 31.0, 28.1, 25.3, 24.6 (C-2' – C-4', C-7' – C-13'), 15.3 (C-14'). $[\alpha]^{20}_D$ = +9.8 (c = 1.0, MeOH). IR/cm^{-1}: 3200, 2870, 2509, 1456, 1398, 1317, 1246, 1101. HRMS: found 376.30575 $[C_{20}H_{41}NO_5+H]^+$, calculated for $[C_{20}H_{41}NO_5+H]^+$ 376.30575.

N-Hydroxyethyl- L-*manno*-1-deoxynojimycin (137)



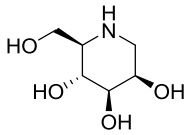
137 (4 mg, 0.02 mmol) was synthesized as described for the preparation of compound for **90a** in a yield of 40%. ^{1}H NMR (400 MHz, MeOD) δ 3.93 (td, *J* = 3.8, 1.8 Hz, 1H, H-2), 3.89 (dd, *J* = 11.1, 4.5 Hz, 1H, H-6a), 3.82 (dd, *J* = 11.1, 3.1 Hz, 1H, H-6b), 3.79 (dd, *J* = 11.5, 4.5 Hz, 1H, H-2'a), 3.72 (t, *J* = 9.8 Hz, 1H, H-4) 3.69 (dd, *J* = 11.7, 4.8 Hz, 1H, H-2'b), 3.50 (dd, *J* = 9.3, 3.2 Hz, 1H, H-3), 3.15 (dd, *J* = 12.6, 4.0 Hz, 1H, H-1a), 3.10 (dd, *J* = 13.9, 2.8 Hz, 1H, H-1'a), 2.85 (dd, *J* = 13.9, 1.6 Hz, 1H, H-1'b), 2.63 – 2.56 (m, 1H, H-1b), 2.49 (ddd, *J* = 9.9, 4.5, 3.1 Hz, 1H, H-5). ^{13}C NMR (100 MHz, MeOD) δ 77.5 (C-3), 70.7 (C-2), 70.3 (C-4), 63.6 (C-5), 62.8 (C-6), 60.8 (C-2'), 56.3 (C-1), 51.2 (C-1'). HRMS: found 208.11791 $[C_8H_{17}NO_5+H]^+$, calculated for $[C_8H_{17}NO_5+H]^+$ 208.11795

2,3,4-Tri-*O*-benzyl- D-*manno*-1-deoxynojimycin (138a):



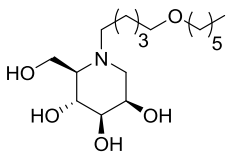
2,3,4-Tri-*O*-benzyl-5-*tert*-butyldimethylsilyl-*O*-D-*manno*-1-deoxynojimycin (0.84 g, 1.25 mmol) was dissolved in THF (8 mL) at r.t.. TBAF (1M in THF, 3.6 mL) was added to the solution under argon protection. The reaction mixture was stirred overnight, diluted with DCM, washed with water and brine, dried (Na_2SO_4) filtered and concentrated. The residual syrup was purified with silica gel column chromatography (20:1, DCM:MeOH) to give the protected **138a** (0.39 g, 0.9 mmol) with 72% yield. R_F = 0.45 (10:1, DCM:MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 15H, H_{Ar} Bn), 4.95 (d, *J* = 11.0 Hz, 1H, CH*H* Bn), 4.70 (d, *J* = 3.6 Hz, 2H, CH_2 Bn), 4.66 – 4.58 (m, 3H, 3 x CH*H* Bn), 3.82 (dd, *J* = 11.0, 3.4 Hz, 1H, H-6a), 3.80 (dd, *J* = 3.1, 1.3 Hz, 1H, H-2), 3.74 (t, *J* = 9.4 Hz, 1H, H-4), 3.62 (dd, *J* = 11.0, 5.9 Hz, 1H, H-6b), 3.53 (dd, *J* = 9.1, 2.9 Hz, 1H, H-3), 3.16 (dd, *J* = 14.2, 3.1 Hz, 1H, H-1a), 2.59 (ddd, *J* = 9.4, 5.8, 3.4 Hz, 1H, H-5), 2.51 (dd, *J* = 14.3, 1.4 Hz, 1H, H-1b), 2.41 (s, 1H, -OH). ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.5 – 128.6 (C_{Ar} Bn), 85.0 (C-3), 78.0 (C-4), 76.2 (CH_2 Bn), 74.6 (C-2), 72.9 (CH_2 Bn), 72.6 (CH_2 Bn), 63.5 (C-6), 62.4 (C-5), 47.7 (C-1).

D-*Manno*-1-deoxynojimycin (138):



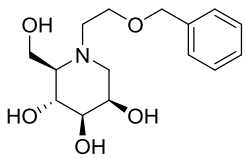
138a (0.39 g, 0.9 mmol) was dissolved in ethanol (50 mL), and pH of the solution was adjusted to 2 with aqueous HCl (1M). After the solvent flushed with argon (3 x), a catalyst amount of Pd/C (10%) was added. The reaction mixture was exposed to H_2 atmosphere (2 bar) for 18 hours. After TLC analysis showed completely consumption **138a**, the reaction mixture was filtered over a pad of Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% → 20% methanol in DCM + 1% NH_4OH) to give **138** in a yield of 60% (0.09 g, 0.54 mmol). ^{1}H NMR (400 MHz, MeOD) δ 4.16 (td, *J* = 3.1, 1.6 Hz, 1H, H-2), 4.02 (dd, *J* = 11.8, 3.3 Hz, 1H, H-6a), 3.84 (dd, *J* = 10.3, 9.3 Hz, 1H, H-4), 3.83 (dd, *J* = 11.9, 7.0 Hz, 1H, H-1b), 3.61 (dd, *J* = 9.2, 3.0 Hz, 1H, H-3), 3.35 (dd, *J* = 13.5, 3.2 Hz, 1H, H-1a), 3.24 (dd, *J* = 13.2, 1.6 Hz, 1H, H-1b), 3.08 (ddd, *J* = 10.3, 7.0, 3.3 Hz, 1H, H-5). ^{13}C NMR (100 MHz, MeOD) δ 75.3 (C-3), 68.4 (C-4), 68.4 (C-2), 63.3 (C-5), 60.5 (C-6), 49.8 (C-1).

N-[5-(Hexyloxy)pentyl]-D-*manno*-1-deoxynojimycin (142):



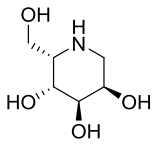
138 was subjected to the general procedure A and generated **142** (6.4 mg, 0.02 mmol) in a yield of 7%. ^{1}H NMR (400 MHz, MeOD) δ 4.05 – 4.03 (m, 1H, H-2), 4.03 (dd, *J* = 12.2, 3.1 Hz, 1H, H-6a), 3.95 (dd, *J* = 12.3, 2.9 Hz, 1H, H-6b), 3.86 (t, *J* = 9.2 Hz, 1H, H-4), 3.55 – 3.49 (m, 1H, H-3), 3.48 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.46 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.33 – 3.27 (m, 2H, H_2-1'), 3.18 – 2.99 (m, 2H, H_2-1), 1.78 – 1.27 (m, 14H, H_2-2', H_2-3', H_2-4', H_2-7', H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 75.8 (C-3), 72.9 (C-6'), 72.4 (C-5'), 68.3 (C-4), 68.3 (C-2), 58.0 (C-6), 56.6 (C-1'), 54.9 (C-1), 33.7, 31.6, 31.2, 27.8, 25.6, 25.2, 24.6 (C-2' – C-4', C-7' – C-10'), 15.2 (C-11'). IR/cm^{-1}: 3302, 2930, 2858, 2046, 1684, 1456, 1269, 1105. HRMS: found 334.25890 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

N-Benzyloxyethyl-D-*manno*-1-deoxynojimycin (145):



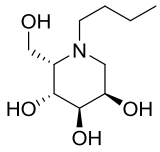
138 was subjected to the general procedure A and generated **145** (4.8 mg, 0.015 mmol) in a yield of 5%. ^{1}H NMR (400 MHz, MeOD) δ 7.48 – 7.31 (m, 5H, H_{Ar} Bn), 4.53 (s, 2H, CH_2 Bn) 4.33 (d, *J* = 13.2 Hz, 1H, H-2'a), 4.18 (dd, *J* = 11.8, 2.9 Hz, 1H). 4.03 (dd, *J* = 11.9, 2.8 Hz, 1H, H-6a), 3.97 (dd, *J* = 11.9, 2.7 Hz, 1H, H-6b), 3.90 (td, *J* = 3.7, 1.7 Hz, 1H, H-2), 3.75 (t, *J* = 9.1 Hz, 1H, H-4), 3.45 – 3.41 (m, 2H, H-2'b, H-3), 3.15 (dd, *J* = 12.5, 3.8 Hz, 1H, H-1a), 3.23 – 3.14 (m, 1H, H-1'a), 2.97 – 2.90 (m, 1H, H-1'b), 2.72 (dd, *J* = 12.4, 1.6 Hz, 1H, H-1b), 2.37 (dt, *J* = 9.0, 2.7 Hz, 1H, H-5). ^{13}C NMR (100 MHz, MeOD) δ 140.4 – 129.6 (C_{Ar} Bn), 77.3 (C-3), 75.1 (CH_2 Bn), 70.3 (C-2), 70.2 (C-4), 68.3 (C-5), 60.3 (C-6), 59.1 (C-2'), 57.9 (C-1), 53.7 (C-1'). IR/cm^{-1}: 3360, 2504, 1636, 1558, 1506, 1456, 1435, 1271, 1207, 1082, 1051. HRMS: found 298.16504 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

L-*Gulo*-1-deoxynojimycin (146):



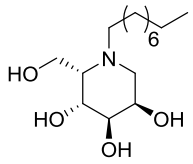
146 (0.15 g, 0.90 mmol) was synthesized as described for the preparation of compound **138** in a yield of 59%**.** ^{1}H NMR (400 MHz, MeOD) δ 4.22 (ddd, *J* = 11.5, 5.1, 2.7 Hz, 1H, H-2), 4.02 (dd, *J* = 4.6, 1.6 Hz, 1H, H-4), 3.99 (dd, *J* = 4.5, 2.8 Hz, 1H, H-3), 3.85 (dd, *J* = 11.8, 5.5 Hz, 1H, H-6a), 3.81 (dd, *J* = 11.8, 8.2 Hz, 1H, H-6b), 3.47 (ddd, *J* = 7.6, 5.5, 1.6 Hz, 1H, H-5), 3.18 (dd, *J* = 11.8, 5.1 Hz, 1H, H-1a), 3.08 (t, *J* = 11.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 69.0 (C-3), 67.4 (C-4), 62.6 (C-2), 59.2 (C-6), 55.6 (C-5), 42.7 (C-1). $[\alpha]^{20}_D$ = -24.8 (c = 1.0, MeOH). IR/cm^{-1}: 3350, 3034, 1634, 1436, 1126, 1078, 1051, 1015. HRMS: found 164.09164 $[C_6H_{13}NO_4+H]^+$, calculated for $[C_6H_{13}NO_4+H]^+$ 164.09173.

N-Butyl-L-*gulo*-1-deoxynojimycin (147):



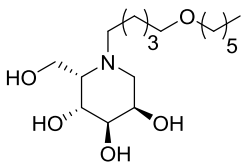
146 was subjected to the general procedure A and generated **147** (7 mg, 0.03 mmol) in a yield of 35%. ^{1}H NMR (600 MHz, MeOD) δ 4.16 – 4.12 (m, 1H, H-2), 4.06 (dd, *J* = 4.9, 2.4 Hz, 1H, H-4), 3.97 (dd, *J* = 11.9, 5.0 Hz, 1H, H-6a), 3.94 (d, *J* = 5.0 Hz, 1H, H-6b), 3.89 (dd, *J* = 4.7, 3.1 Hz, 1H, H-3), 3.15 – 2.81 (m, 5H, H-5, H_2-1', H_2-1), 1.76 – 1.60 (m, 2H, H_2-2'), 1.46 – 1.42 (m, 2H, H_2-3'), 1.06 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (150 MHz, MeOD) δ 73.5 (C-4), 72.4 (C-3), 66.9 (C-2), 62.1 (C-6), 62.0 (C-5), 55.5 (C-1'), 53.3 (C-1), 26.3 (C-2'), 22.4 (C-3'), 15.1 (C-4'). $[\alpha]^{20}_D$ = +55.0 (c = 0.1, MeOH). IR/cm^{-1}: 3335, 2974, 2928, 2900, 2349, 1636, 1456, 1379, 1271, 1083, 1043. HRMS: found 220.15440 $[C_{10}H_{21}NO_4+H]^+$, calculated for $[C_{10}H_{21}NO_4+H]^+$ 220.15433.

N-Nonyl-L-*gulo*-1-deoxynojimycin (148):



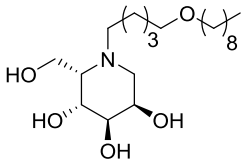
146 was subjected to the general procedure A and generated **148** (8 mg, 0.03 mmol) in a yield of 31%. ^{1}H NMR (400 MHz, MeOD) δ 4.22 (ddd, *J* = 9.0, 6.3, 2.9 Hz, 1H, H-2), 4.11 (dd, *J* = 4.7, 2.1 Hz, 1H, H-4), 4.01 (dd, *J* = 12.0, 4.7 Hz, 1H, H-6a), 3.97 (dd, *J* =12.0, 5.0 Hz, 1H, H-6b), 3.93 (dd, *J* = 4.6, 2.9 Hz, 1H, H-3), 3.34 (td, *J* = 4.8, 2.2 Hz, 1H, H-5), 3.18 (ddd, *J* = 9.5, 6.7, 2.3 Hz, 2H, H_2-1'), 3.15 – 3.10 (m, 2H, H_2-1), 1.93 – 1.69 (m, 2H, H_2-2'), 1.54 – 1.33 (m, 12H, H_2-3' – H_2-8'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 72.6 (C-4), 71.2 (C-3), 65.3 (C-2), 62.0 (C-5), 61.3 (C-6), 55.0 (C-1'), 52.0 (C-1), 33.4, 30.8, 30.8, 28.3, 28.3, 24.3 (C-2' – C-8'), 14.9 (C-9'). $[\alpha]^{20}_D$ = +14.4 (c = 0.5, MeOH). IR/cm^{-1}: 3336, 2925, 2854, 1653, 1468, 1378, 1145, 1064, 979, 667. HRMS: found 290.23272 $[C_{15}H_{31}NO_4+H]^+$, calculated for $[C_{15}H_{31}NO_4+H]^+$ 290.23258.

N-[5-(Hexyloxy)pentyl]-L-*gulo*-1-deoxynojimycin (149):



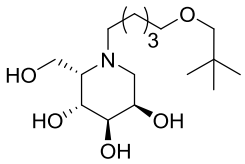
146 was subjected to the general procedure A and generated **149** (9 mg, 0.03 mmol) in a yield of 30%. ^{1}H NMR (400 MHz, MeOD) δ 4.14 (ddd, *J* = 10.2, 4.5, 3.0 Hz, 1H, H-2), 4.06 (dd, *J* = 4.8, 2.3 Hz, 1H, H-4), 3.98 (dd, *J* = 11.7, 4.7 Hz, 1H, H-6a), 3.94 (d, *J* = 12.0, 4.5 Hz, 1H), 3.89 (dd, *J* = 4.7, 3.1 Hz, 1H, H-3), 3.53 (t, *J* = 6.5 Hz, 2H, H_2-5'), 3.51 (t, *J* = 6.6 Hz, 2H, H_2-6') , 3.23 – 2.85 (m, 5H, H-5, H_2-1', H_2-1), 1.90 – 1.31 (m, 14H, H_2-2', H_2-3', H_2-4', H_2-7', H_2-8', H_2-9', H_2-10'), 0.94 (t, *J* = 7.0 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 73.0 (C-4), 72.8 (C-6'), 72.4 (C-5'), 72.1 (C-3), 66.8 (C-2), 62.0 (C-6), 62.0 (C-5), 55.5 (C-1'), 53.1 (C-1), 33.4, 31.2, 31.1, 27.6, 25.4, 25.2, 24.3 (C-2' – C-4', C-7' – C-10'), 15.0 (C-11'). $[\alpha]^{20}_D$ = +27.0 (c = 0.1, MeOH). IR/cm^{-1}: 3380, 2987, 2872, 2376, 1635, 1506, 1456, 1394, 1229, 1076. HRMS: found 334.25886 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

N-[5-(Nonyloxy)pentyl]-L-*gulo*-1-deoxynojimycin (150):



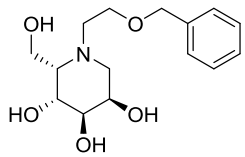
146 was subjected to the general procedure A and generated **150** (8 mg, 0.02 mmol) in a yield of 24%. ^{1}H NMR (400 MHz, MeOD) δ 4.28 (ddd, *J* = 11.1, 5.2, 2.8 Hz, 1H, H-2), 4.17 (dd, *J* = 4.4, 1.7 Hz, 1H, H-4), 4.06 (dd, *J* = 12.9, 4.1 Hz, 1H, H-6a), 4.01 (dd, *J* = 12.9, 4.8 Hz, 1H, H-6b), 3.97 (dd, *J* = 4.1, 3.0 Hz, 1H, H-3), 3.58 – 3.55 (m, 1H, H-5), 3.55 (t, *J* = 5.5 Hz, 2H, H_2-5'), 3.52 (t, *J* = 6.3 Hz, 2H, H_2-6'), 3.39 – 3.30 (m, 2H, H_2-1'), 3.31 – 3.20 (m, 2H, H_2-1), 3.71 – 3.64 (m, 2H, H_2-2'), 2.01 – 1.81 (m, 2H, H_2-7'), 1.77 – 1.70 (m, 2H, H_2-4'), 1.71 – 1.62 (m, 2H, H_2-3'), 1.63 – 1.48 (m, 12H, H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.94 (t, *J* = 7.0 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 73.2 (C-4), 72.9 (C-6'), 72.3 (C-5'), 70.9 (C-3), 65.0 (C-2), 62.6 (C-5), 62.0 (C-6), 55.8 (C-1'), 52.1 (C-1), 33.9, 31.9, 31.6, 31.6, 31.5, 31.3, 31.0, 28.1, 25.4, 23.9 (C-2' –C-4', C-7' – C-13'), 15.2 (C-14'). IR/cm^{-1}: 3308, 2927, 2872, 2313, 1636, 1456, 1394, 1204, 1057. $[\alpha]^{20}_D$ = +6.5 (c = 0.2, MeOH). HRMS: found 376.30576 $[C_{20}H_{41}NO_5+H]^+$, calculated for $[C_{20}H_{41}NO_5+H]^+$ 376.30575.

N-[5-(3,3-Dimethyl-1-propyloxy)pentyl]-L-*gulo*-1-deoxynojimycin (151):



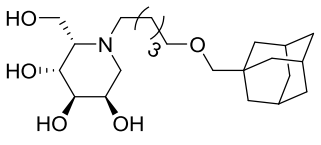
146 was subjected to the general procedure A and generated **151** (8 mg, 0.03 mmol) in a yield of 28%. ^{1}H NMR (600 MHz, MeOD) δ 4.09 (dd, *J* = 9.0, 4.8 Hz, 1H, H-2), 4.03 (td, *J* = 4.4, 2.1 Hz, 1H, H-4), 3.94 (dd, *J* = 11.7, 5.2 Hz, 1H, H-6a), 3.90 (dd, *J* = 11.6, 4.8 Hz, 1H, H-6b), 3.86 (dd, *J* = 4.8, 3.2 Hz, 1H, H-3), 3.51 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.16 (s, 2H, H_2-6'), 2.99 – 2.75 (m, 5H, H-5, H_2-1', H_2-1), 1.79 – 1.62 (m, 4H, H_2-4', H_2-2'), 1.50 – 1.41 (m, 2H, H_2-3'), 0.99 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (150 MHz, MeOD) δ 83.4 (C-6'), 73.6 (C-4), 73.2 (C-5'), 72.7 (C-3), 67.9 (C-2), 62.4 (C-6), 61.8 (C-5), 55.7 (C-1'), 53.6 (C-1), 33.8 (C-7'), 31.4 (C-4'), 28.0 (C-8', C-9', C-10'), 26.1 (C-2'), 25.4 (C-3'). $[\alpha]^{20}_{D}$ = +29.0 (c = 0.1, MeOH). IR/cm^{-1}: 3422, 2953, 2900, 2866, 2374, 2349, 2312, 1683, 1506, 1394, 1373, 1317, 1074. HRMS: found 320.24327 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

N-Benzyloxyethyl-L-*gulo*-1-deoxynojimycin (152a):



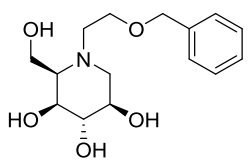
146 was subjected to the general procedure A and generated **152a** (13 mg, 0.04 mmol) in a yield of 22%. ^{1}H NMR (400 MHz, MeOD) δ 7.52 – 7.29 (m, 5H, H_{Ar} Bn), 4.63 (s, 2H, CH_2 Bn), 4.01 – 3.99 (m, 1H, H-2), 3.95 (dd, *J* = 11.7, 4.9 Hz, 1H, H-6a), 3.90 (dd, *J* = 11.7, 5.4 Hz, 1H, H-6b), 3.84 (td, *J* = 5.0, 2.6 Hz, 1H, H-3), 3.76 (dd, *J* = 5.2, 3.5 Hz, 1H, H-4), 3.59 (d, *J* = 13.5 Hz, 1H, H-2'a), 3.24 – 3.12 (m, 1H, H-1'a), 3.07 – 3.00 (m, 2H, H-1'b, H-2'b), 2.91 (t, *J* = 5.3 Hz, 1H, H-5), 2.76 (dd, *J* = 11.4, 4.3 Hz, 1H, H-1a), 2.46 (dd, *J* = 11.1, 9.6 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 131.9 – 129.6 (CH_{Ar} Bn), 75.1 (CH_2 Bn), 73.5 (C-3), 69.0 (C-4), 68.4 (C-2), 63.1 (C-5), 62.2 (C-6), 60.0 (C-2'), 54.4 (C-1'), 53.4 (C-1). $[\alpha]^{20}_{D}$ = +35.2 (c = 0.5, MeOH). IR/cm^{-1}: 3345, 2924, 1653, 1506, 1457, 1201, 1074, 1037. HRMS: found 298.16500 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

N-[5-(Adamantan-1-yl-methoxy)pentyl]-L-*gulo*-1-deoxynojimycin (79):



146 was subjected to the general procedure A and generated **79** (7 mg, 0.02 mmol) in a yield of 19%. ^{1}H NMR (400 MHz, MeOD) δ 4.16 (ddd, *J* = 10.1, 4.8, 3.0 Hz, 1H, H-2), 4.07 (dd, *J* = 4.7, 2.3 Hz, 1H, H-4), 3.90 (dd, *J* = 4.7, 3.1 Hz, 1H, H-3), 3.99 (dd, *J* = 12.0, 4.9 Hz, 1H,), 3.94 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.59 (t, *J* = 7.3 Hz, 2H, H_2-5'), 3.54 (t, *J* = 6.2 Hz, 2H, H_2-6'), 3.14 (td, *J* = 4.7, 2.0 Hz, 1H, H-5), 3.11 – 3.02 (m, 2H, H_2-1'), 3.00 (dd, *J* = 11.2, 4.9 Hz, 1H, H-1a), 2.93 (t, *J* = 10.7 Hz, 1H, H-1b), 2.04 – 2.02 (m, 3H, 3 x CH ada), 1.89 – 1.72 (m, 8H, 3 x CH_2 ada, H_2-2'), 1.72 – 1.61 (m, 8H, 3 x CH_2 ada, H_2-3'), 1.46 (td, *J* = 7.3, 3.4 Hz, 2H, H-4'). ^{13}C NMR (100 MHz, MeOD) δ 73.4 (C-4), 72.2 (C-3), 72.2 (C-6'), 68.7 (C-5'), 66.5 (C-2), 62.0 (C-5), 61.6 (C-6), 55.4 (C-1'), 53.1 (C-1), 45.6 (C-4'), 44.7 (CH_2 ada), 39.1 (CH_2 ada), 33.7 (C_q ada), 31.0 (CH ada), 29.2 (C-3'), 20.5 (C-2'). $[\alpha]^{20}_{D}$ = +18.0 (c = 0.1, MeOH). IR/cm^{-1}: 3300, 2978, 2901, 2349, 1635, 1489, 1259, 1082, 1045, 878. HRMS: found 398.29004 $[C_{22}H_{39}NO_5+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.29010.

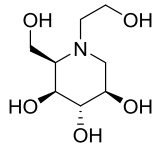
N-Benzyloxyethyl-D-*ido*-1-deoxynojimycin (157):



D-*ido*-DNJ was subjected to the general procedure A and generated **157** (44.8 mg, 0.15 mmol) in a yield of 25%. ^{1}H NMR (400 MHz, MeOD) δ 7.47 – 7.30 (m, 5H, H_{Ar} Bn), 4.62 (s, 2H, CH_2 Bn), 4.00 (dd, *J* = 11.6, 9.6 Hz, 1H, H-6a), 3.92 (dd, *J* = 11.6, 8.8 Hz, 1H, H-6b), 3.81 (dd, *J* = 8.9, 5.3 Hz, 1H, H-4), 3.69 (t, *J* = 5.7 Hz, 2H, H_2-2'), 3.67 – 3.61 (m, 1H, H-2), 3.45 (t, *J* = 8.5 Hz, 1H, H-3), 3.17 (q, *J* = 5.5 Hz, 1H, H-5), 3.11 (t, *J* = 5.6 Hz, 1H, H-1'a), 3.03 (t, *J* = 5.6 Hz, 1H, H-1'b), 2.97 (dd, *J* = 13.0, 5.1 Hz, 1H, H-1a), 2.74 (dd, *J* = 11.9, 9.1 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 140.4 – 128.9 (C_{Ar} Bn), 76.7 (C-3), 75.0 (CH_2 Bn), 73.3 (C-4), 71.9 (C-2), 70.7 (C-2'), 65.9 (C-5), 58.8 (C-6), 56.1 (C-1'), 53.7 (C-1). IR/cm^{-1}: 3330,

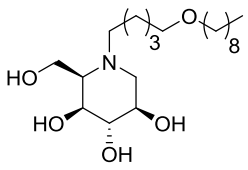
2950, 1653, 1456, 1362, 1272, 1209, 1058, 1027, 735. $[\alpha]^{20}_D$ = +18.0 (c = 1.0, MeOH). HRMS: found 298.16501 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

N-Hydroxyethyl-D-*ido*-1-deoxynojimycin (158):



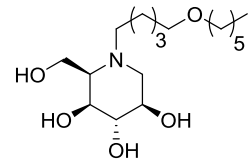
158 (12.1 mg, 0.06 mmol) was synthesized as described for the preparation of compound **90a** in a yield of 30%. ^{1}H NMR (400 MHz, MeOD) δ 4.15 (br s, 1H, H-3), 4.13 – 3.95 (m, 5H, H_2-6 H-2'a, H-2, H-4), 3.91 (dd, *J* = 11.9, 5.1 Hz, 1H, H-2'b), 3.78 (t, *J* = 5.0 Hz, 1H, H-5), 3.72 (d, *J* = 13.5 Hz, 1H, H-1a), 3.58 – 3.49 (m, 1H, H-1b), 3.46 (d, *J* = 13.3 Hz, 1H, H-1'a), 3.34 (dd, *J* = 13.4, 2.4 Hz, 1H, H-1'b). ^{13}C NMR (100 MHz, MeOD) δ 72.8 (C-3), 69.9 (C-4), 68.7 (C-2), 65.5 (C-5), 61.4 (C-2'), 57.4 (C-6), 57.4 (C-1), 47.7 (C-1'). $[\alpha]^{20}_D$ = -6.0 (c = 0.2, MeOH). IR/cm^{-1}: 3421, 2987, 2901, 2374, 1684, 1558, 1506, 1456, 1317, 1074. HRMS: found 208.11790 $[C_8H_{17}NO_5+H]^+$, calculated for $[C_8H_{17}NO_5+H]^+$ 208.11795.

N-[5-(Nonyloxy)pentyl]-D-*ido*-1-deoxynojimycin (159):



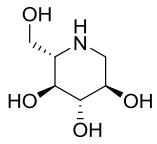
D-*ido*-DNJ (**153**) was subjected to the general procedure A and generated **159** (36.2 mg, 0.10 mmol) in a yield of 20%. ^{1}H NMR (400 MHz, MeOD) δ 3.94 (dd, *J* = 11.5, 4.8 Hz, 1H, H-6a), 3.90 (dd, *J* = 11.4, 6.4 Hz, 1H, H-6b), 3.78 (dd, *J* = 8.8, 5.2 Hz, 1H, H-4), 3.62 (ddd, *J* = 9.4, 8.0, 4.9 Hz, 1H, H-2), 3.52 (t, *J* = 6.5 Hz, 2H, H_2-5'), 3.51 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.46 (t, *J* = 8.4 Hz, 1H, H-3), 3.15 – 3.08 (m, 1H, H-5), 2.89 (dd, *J* = 12.4, 4.8 Hz, 1H, H-1a), 2.86 – 2.83 (m, 1H, H-1'a), 2.79 – 2.70 (m, 1H, H-1'b), 2.67 (dd, *J* = 12.4, 9.5 Hz, 1H, H-1b), 1.75 – 1.54 (m, 6H, H_2-2', H_2-4', H_2-7'), 1.53 – 1.26 (m, 14H, H_2-3', H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 76.7 (C-3), 73.6 (C-4), 72.8 (C-6'), 72.7 (C-5'), 72.1 (C-2), 65.2 (C-5), 58.5 (C-6), 56.4 (C-1'), 53.7 (C-1), 33.9, 31.6, 31.6, 31.5, 31.3, 29.3, 28.1, 25.8, 24.6 (C-2' – C-4', C-7' – C-13'), 15.3 (C-14'). $[\alpha]^{20}_D$ = +24.9 (c = 1.0, MeOH). HRMS: found 376.30605 $[C_{20}H_{41}NO_5+H]^+$, calculated for $[C_{20}H_{41}NO_5+H]^+$ 376.30575.

N-[5-(Hexyloxy)pentyl]-D-*ido*-1-deoxynojimycin (160):



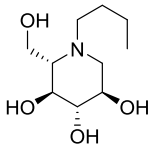
D-*ido*-DNJ (**153**) was subjected to the general procedure A and generated **160** (40.8 mg, 0.12 mmol) in a yield of 20%. ^{1}H NMR (400 MHz, MeOD) δ 4.20 – 3.86 (m, 5H, H-2, H_2-6, H-4, H-3), 3.64 (br s, 1H, H-5), 3.57 – 3.53 (m, 1H, H-1a), 3.55 (t, *J* = 6.3 Hz, 1H, H-5'), 3.52 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.49 – 3.40 (m, 3H, H_2-1', H-1b), 2.07 – 1.78 (m, 2H, H_2-2'), 1.78 – 1.69 (m, 2H, H_2-4'), 1.66 – 1.64 (m, 2H, H_2-7'), 1.60 – 1.51 (m, 2H, H_2-3'), 1.50 – 1.28 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 73.0 (C-2), 72.9 (C-6'), 72.3 (C-5'), 69.7 (C-4), 68.9 (C-3), 64.7 (C-5), 62.2 (C-6), 56.2 (C-1'), 55.9 (C-1), 33.7 , 31.6, 31.0, 27.8, 25.3, 25.3, 24.5 (C-2' – C-4', C-7' – C-10'), 15.3 (C-11'). $[\alpha]^{20}_D$ = -4.2 (c = 1.0, MeOH). IR/cm^{-1}: 3385, 2932, 2859, 1628, 1435, 1269, 1096, 1067. HRMS: found 334.25887 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

L-*Gluco*-1-deoxynojimycin (161):



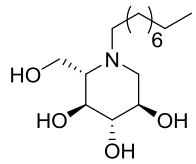
^{1}H NMR (400 MHz, MeOD) δ 3.93 (dd, *J* = 11.8, 3.3 Hz, 1H, H-6a), 3.85 (dd, *J* = 11.8, 5.5 Hz, 1H, H-6b), 3.69 (ddd, *J* = 11.4, 9.1, 5.1 Hz, 1H, H-2), 3.51 (dd, *J* = 10.4, 9.0 Hz, 1H, H-4), 3.38 (t, *J* = 9.1 Hz, 1H, H-3), 3.34 (dd, *J* = 12.4, 5.1 Hz, H-1a), 3.06 (ddd, *J* = 10.4, 5.5, 3.3 Hz, 1H, H-5), 2.87 (dd, *J* = 12.4, 11.4 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 77.1 (C-3), 68.3 (C-4), 67.5(C-2), 60.5 (C-5), 57.9 (C-6), 46.4 (C-1). $[\alpha]^{20}_D$ = -34.8 (c = 1.0, MeOH). IR/cm^{-1}: 3315, 2945, 2497, 1616, 1417, 1093, 1043, 1022. HRMS: found 164.09172 $[C_6H_{13}NO_4+H]^+$, calculated for $[C_6H_{13}NO_4+H]^+$ 164.09173.

N-Butyl-L-*gluco*-1-deoxynojimycin (162):



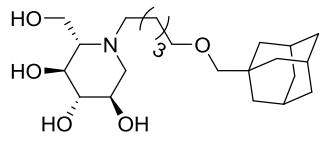
161 was subjected to the general procedure A and generated **162** (53.9 mg, 0.25 mmol) in a yield of 40%. ^{1}H NMR (400 MHz, MeOD) δ 4.12 (dd, *J* = 12.5, 1.9 Hz, 1H, H-6a), 3.94 (dd, *J* = 12.5, 3.1 Hz, 1H, H-6b), 3.73 (ddd, *J* = 11.2, 9.2, 4.9 Hz, 1H, H-2), 3.62 (dd, *J* = 10.3, 9.2 Hz, 1H, H-4), 3.47 (dd, *J* = 12.1, 4.9 Hz, 1H, H-1), 3.40 (t, *J* = 9.3 Hz, 1H, H-3), 3.33 (m, 1H, H-1'a), 3.22 (dt, *J* = 12.7, 6.5 Hz, 1H, H-1'b), 3.06 (d, *J* = 10.2 Hz, 1H, H-5), 2.99 (t, *J* = 11.7 Hz, 1H, H-1b), 1.78 – 17.4 (m, 2H, H_2-2'), 1.47 – 1.45 (m, 2H, H_2-3'), 1.04 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (100 MHz, MeOD) δ 76.8 (C-3), 66.5 (C-4), 67.6 (C-2), 66.1 (C-5), 53.7 (C-6), 52.4 (C-1), 52.7 (C-1'), 24.9 (C-2'), 19.6 (C-3'), 12.6 (C-4'). IR/cm^{-1}: 3320, 3038, 2962, 2873, 1653, 1398, 1099, 1086, 1050, 1028, 936, 886. $[\alpha]^{20}_{D}$ = +1.2 (c = 1.0, MeOH). HRMS: found 220.15428 $[C_{10}H_{21}NO_4+H]^+$, calculated for $[C_{10}H_{21}NO_4+H]^+$ 220.15433.

N-Nonyl-L-*gluco*-1-deoxynojimycin (163):



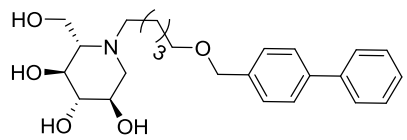
161 was subjected to the general procedure A and generated **163** (63.5 mmol, 0.22 mmol) in a yield of 37%. ^{1}H NMR (400 MHz, MeOD) δ 4.10 (d, *J* = 12.5 Hz, 1H, H-6a), 3.92 (dd, *J* = 12.4, 3.0 Hz, 1H, H-6b), 3.69 (td, *J* = 10.3, 4.7 Hz, 1H, H-2), 3.59 (t, *J* = 9.7 Hz, 1H, H-4), 3.42 (dd, *J* = 12.1, 4.7 Hz, 1H, H-1a), 3.37 (t, *J* = 9.2 Hz, 1H, H-3), 3.32 – 3.24 (m, 1H, H-1'a), 3.20 – 3.10 (m, 1H, H-1'b), 3.02 – 2.84 (m, 2H, H-5, H-1b), 1.88 – 1.61 (m, 2H, H_2-2'), 1.51 – 1.24 (m, 12H, H_2-3', H_2-4', H_2-5', H_2-6', H_2-7', H_2-8'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) 77.0 (C-3), 67.7 (C-4), 66.7 (C-2), 66.0 (C-5), 54.0 (C-6), 53.7 (C-1), 52.8 (C-1'), 31.6, 29.1, 28.9, 28.9, 26.4, 22.9, 22.3 (C-2'- C-8'), 13.0 (C-9'). $[\alpha]^{20}_{D}$ = +4.3 (c = 1.0, MeOH). IR/cm^{-1}: 3333, 2924, 2855, 1456, 1374, 1085, 1026, 952, 886, 721. HRMS: found 290.23260 $[C_{15}H_{31}NO_4+H]^+$, calculated for $[C_{15}H_{31}NO_4+H]^+$ 290.23258.

N-[5-(adamantan-1-yl-methoxy)pentyl]-L-*gluco*-1-deoxynojimycin (76):



161 was subjected to the general procedure A and generated **76** (11 mg, 0.03 mmol) in a yield of 14%. ^{1}H NMR (400 MHz, MeOD) δ 3.96 (d, *J* = 2.7 Hz, 2H, H_2-6), 3.58 (ddd, *J* = 10.6, 9.1, 4.9 Hz, 1H, H-2), 3.48 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.40 (t, *J* = 9.2 Hz, 1H, H-4), 3.24 (t, *J* = 9.1 Hz, 1H, H-3), 3.12 (dd, *J* = 11.3, 4.9 Hz, 1H, H-1a), 2.94 (ddd, *J* = 13.4, 9.6, 6.7 Hz, 1H, H-1'a), 2.74 (ddd, *J* = 13.3, 9.4, 6.1 Hz, 1H, H-1'b), 2.35 (t, *J* = 11.0 Hz, 1H, H-1b), 2.30 (dt, *J* = 9.6, 2.8 Hz, 1H, H-5), 2.05 – 2.03 (m, 3H, 3 x CH ada), 1.89 – 1.74 (m, 6H, 3 x CH_2 ada), 1.65 (d, *J* = 2.8 Hz, 6H, 3 x CH_2 ada), 1.72 – 1.59 (m, 4H, H_2-2', H_2-4'), 1.54 – 1.37 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 83.9 (C-6'), 81.2 (C-3), 73.3 (C-5'), 72.6 (C-4), 71.3 (C-2), 68.2 (C-5), 59.8 (C-6), 58.3 (C-1), 54.7 (C-1'), 41.7 (CH_2 ada), 39.2 (CH_2 ada), 36.0 (C_q ada), 31.4 (C-4'), 30.6 (CH ada), 26.1 (C-2'), 25.8 (C-3'). $[\alpha]^{20}_{D}$ = +6.4 (c = 0.5, MeOH). HRMS: found 398.28980 $[C_{22}H_{39}NO_5+H]^+$, calculated for $[C_{22}H_{39}NO_5+H]^+$ 398.29010

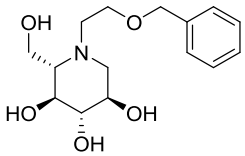
N-[(Biphenyl-4-yl-methoxy)pentyl]-L-*gluco*-1-deoxynojimycin (164):



161 was subjected to the general procedure A and generated **164** (28 mg, 0.07 mmol) in a yield of 22%. ^{1}H NMR (400 MHz, MeOD) δ 7.64 – 7.29 (m, 9H, H_{Ar} BiPh), 3.95 (dd, *J* = 12.0, 2.6 Hz, 1H, H-6a), 3.91 (dd, *J* = 12.0, 2.8 Hz, 1H, H-6b), 3.57 (ddd, *J* = 10.5, 9.1, 4.8 Hz, 1H, H-2), 3.48 – 3.43 (m, 2H, H_2-5'), 3.45 (t, *J* = 9.3 Hz, 1H, H-4), 3.23 (t, *J* = 9.1 Hz, 1H, H-3), 3.07 (dd, *J* = 11.2, 4.9 Hz, 1H, H-1a), 2.86 (dt, *J* = 13.4, 7.5 Hz, 1H, H-1'a), 2.65 (dt, *J* = 15.4, 6.9 Hz, 1H, H-1'b), 2.26 (t, *J* = 10.8 Hz, 1H, H-1b), 2.19 (dt, *J* = 9.5, 2.8 Hz, 1H, H-5), 1.64 (p, *J* = 7.0 Hz, 2H, H_2-4'), 1.56 (p, *J* = 7.8 Hz, 2H, H_2-2'), 1.41 – 1.37 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 144.4 – 129.1 (C_{Ar} BiPh), 81.4 (C-3), 72.8 (C-4), 72.6 (C-6'), 72.3 (C-5'), 71.6 (C-2), 68.1 (C-5), 60.3 (C-6), 58.5 (C-1), 54.5 (C-1'), 31.4 (C-4'), 26.1 (C-3'), 25.8 (C-2'). IR/cm^{-1}: 3322, 2933, 2861, 1646,

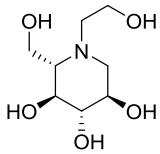
1479, 1456, 1362, 1268, 1198, 1156, 1085, 1034, 1009. $[\alpha]^{20}_D$ = -31.7 (c = 1, MeOH). HRMS: found 416.24299 $[C_{24}H_{33}NO_5+H]^+$, calculated for $[C_{24}H_{33}NO_5+H]^+$ 416.24315.

N-Benzyloxyethyl -L-*gluco*-1-deoxynojimycin (165):



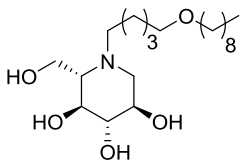
161 was subjected to the general procedure A and generated **165** (13 mg, 0.04 mmol) in a yield of 15%. ^{1}H NMR (400 MHz, MeOD) δ 7.51 – 7.26 (m, 5H, H_{Ar} Bn), 4.62 (s, 2H, CH_2 Bn), 3.99 (dd, *J* = 11.5, 9.9 Hz, 1H, H-6a), 3.91 (t, *J* = 11.4 Hz, 1H, H-6b), 3.81 (dd, *J* = 8.9, 5.3 Hz, 1H, H-4), 3.70 (t, *J* = 5.7 Hz, 2H, H_2-2'), 3.66 – 3.58 (m, 1H, H-2), 3.46 (t, *J* = 8.5 Hz, 1H, H-3), 3.18 (dd, *J* = 11.7, 5.3 Hz, 1H, H-5), 3.13 (dd, *J* = 13.8, 5.6 Hz, H-1'a), 3.03 (dd, *J* = 13.7, 5.6 Hz, H-1'b), 2.98 (dd, *J* = 12.7, 4.9 Hz, 1H, H-1a), (dd, *J* = 12.5, 9.7 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 140.4 – 129.6 (C_{Ar} Bn), 76.6 (C-3), 75.0 (CH_2 Bn), 73.3 (C-4), 71.9 (C-2), 70.4 (C-2'), 65.7 (C-5), 58.8 (C-6), 56.1 (C-1'), 52.7 (C-1). IR/cm^{-1}: 3328, 2878, 1670, 1456, 1362, 1261, 1203, 1136, 1059, 1027. $[\alpha]^{20}_D$ = -9.3 (c = 1.0, MeOH). HRMS: found 298.16502 $[C_{15}H_{23}NO_5+H]^+$, calculated for $[C_{15}H_{23}NO_5+H]^+$ 298.16490.

N-Hydroxyethyl-L-*gluco*-1-deoxynojimycin (166):



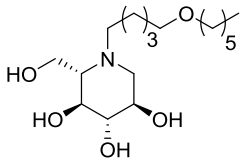
166 (14 mg, 0.07 mmol) was synthesized as described for the preparation of compound **90a** in a yield of 47%. ^{1}H NMR (400 MHz, MeOD) δ 4.17 – 4.11 (m, 1H, H-3), 4.11 – 3.98 (m, 3H, H_2-6, H-2'a), 4.07 (ddd, *J* = 10.4, 6.7, 3.6 Hz, 1H, H-2), 3.99 – 3.93 (m, 1H, H-4), 3.88 (dd, *J* = 11.7, 4.8 Hz, 1H, H-2'b), 3.75 – 3.66 (m, 1H, H-1a), 3.58 – 3.48 (m, 2H, H-5, H-1b), 3.45 (dd, *J* = 13.1, 2.1 Hz, 1H, H-1'a), 3.32 (dd, *J* = 13.4, 3.3 Hz, 1H, H-1'b). ^{13}C NMR (100 MHz, MeOD) δ 73.1 (C-3), 70.1 (C-4), 69.3 (C-2), 61.6 (C-2'), 59.2 (C-5), 57.5 (C-6), 57.4 (C-1), 47.8 (C-1'). IR/cm^{-1}: 3272, 1646, 1318, 1060. HRMS: found 208.11797 $[C_8H_{17}NO_5+H]^+$, calculated for $[C_8H_{17}NO_5+H]^+$ 208.11795.

N-[5-(Nonyloxy)pentyl]-L-*gluco*-1-deoxynojimycin (167):



161 was subjected to the general procedure A and generated **167** (31 mg, 0.08 mmol) in a yield of 26%. ^{1}H NMR (400 MHz, MeOD) δ 4.21 (d, *J* = 12.5 Hz, 1H, H-6a), 4.00 (dd, *J* = 12.5, 3.2 Hz, 1H, H-6b), 3.80 (ddd, *J* = 11.2, 9.3, 4.9 Hz, 1H, H-2), 3.70 (dd, *J* = 10.5 Hz, 1H, H-4), 3.54 (t, *J* = 12.7 Hz, 2H, H-5'), 3.53 (t, *J* = 12.6 Hz, 2H, H_2-6'), 3.60 – 3.43 (m, 3H, H-1a, H-1'a, H-3), 3.31 (td, *J* = 12.6, 5.3 Hz, 1H, H-1'b), 3.17 (dd, *J* = 10.3, 2.8 Hz, H-5, 1H), 3.10 (dd, *J* = 12.2, 11.2 Hz, 1H, H-1b), 1.96 – 1.81 (m, 2H, H_2-2'), 1.79 – 1.69 (m, 2H, H_2-7'), 1.69 – 1.61 (m, 2H, H_2-4'), 1.59 – 1.50 (m, 2H, H_2-3'), 1.50 – 1.30 (m, 12H, H_2-8' – H_2-13'), 0.94 (t, *J* = 7.0 Hz, 3H, H_3-14'). ^{13}C NMR (100 MHz, MeOD) δ 78.9 (C-3), 72.9 (C-6'), 72.2 (C-5'), 69.7 (C-4), 68.7 (C-2), 68.3 (C-5), 55.7 (C-6), 55.7 (C-1), 55.2 (C-1'), 49.9, 33.9, 31.6, 31.6, 31.5, 31.3, 31.0, 28.1, 25.4, 24.8, 24.6 (C-2' – C-4', C-7' – C-13'), 15.3 (C-14'). $[\alpha]^{20}_D$ = +1.6 (c = 1, MeOH). IR/cm^{-1}:3327, 2955, 2854, 1628, 1456, 1101, 1028. HRMS: found 376.30587 $[C_{20}H_{41}NO_5+H]^+$, calculated for $[C_{20}H_{41}NO_5+H]^+$ 376.30575.

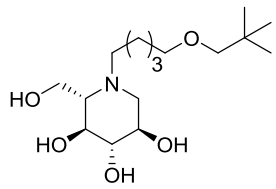
N-[5-(Hexyloxy)pentyl]-L-*gluco*-1-deoxynojimycin (168):



161 was subjected to the general procedure A and generated **168** (12 mg, 0.04 mmol) in a yield of 10%. ^{1}H NMR (400 MHz, MeOD) δ 4.02 (dd, *J* = 12.2, 2.5 Hz, 1H, H-6a), 3.97 (dd, *J* = 12.1, 2.8 Hz, 1H, H-6b), 3.64 (ddd, *J* = 10.7, 7.6, 4.6 Hz, 1H, H-2), 3.52 (t, *J* = 6.4 Hz, 2H, H-5'), 3.51 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.56 – 3.52 (m, 1H, H-4), 3.31 (t, *J* = 9.1 Hz, 1H, H-3), 3.23 (dd, *J* = 11.6, 4.9 Hz, 1H, H-1a), 3.14 – 3.00 (m, 1H, H-1'a), 2.96 – 2.82 (m, 1H, H-1'b), 2.61 – 2.45 (m, 2H, H-1b, H-5), 1.77 – 1.59 (m, 6H, H_2-2', H_2-7', H_2-4'), 1.54 – 1.34 (m, 8H, H_2-3', H_2-8', H_2-9', H_2-10'), 0.94 (t, *J* = 7.0 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 80.6 (C-3), 72.8 (C-6'), 72.5 (C-5'), 71.7 (C-4), 70.6 (C-2), 68.2 (C-5), 58.9 (C-6), 57.6

(C-1), 54.7 (C-1'), 33.7, 31.6, 31.3, 27.8, 25.8, 25.5, 24.5 (C-2' – C-4', C-7' – 10'), 15.3 (C-11'). $[\alpha]^{20}_{D}$ = +9.0 (c = 0.2, MeOH). IR/cm^{-1}: 3361, 2933, 2860, 1670, 1456, 1375, 1202, 1101, 1034. HRMS: found 334.25897 $[C_{17}H_{35}NO_5+H]^+$, calculated for $[C_{17}H_{35}NO_5+H]^+$ 334.25880.

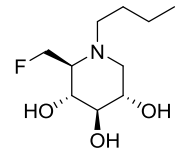
N-[5-(3,3-Dimethyl-1-propyloxy)pentyl]-L-*gluco*-1-deoxynojimycin (169):



161 was subjected to the general procedure A and generated **169** (63 mg, 0.19 mmol) in a yield of 33%. ^{1}H NMR (400 MHz, MeOD) δ 4.06 (dd, *J* = 12.2, 2.2 Hz, 1H, H-6a), 3.98 (dd, *J* = 12.2, 3.0 Hz, 1H, H-6b), 3.67 (td, *J* = 10.5, 9.9, 4.8 Hz, 1H, H-2), 3.56 (t, *J* = 9.7 Hz, 1H, H-4), 3.53 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.34 (t, *J* = 9.1 Hz, 1H, H-3), 3.38 – 3.27 (m, 1H, H-1a), 3.16 (s, 2H, H_2-6'), 3.16 (br s, 1H, H-1'a), 2.67 (br s, 2H, H-1b, H-5), 1.85 – 1.66 (m, 4H, H_2-2', H_2-4'), 1.59 – 1.43 (m, 2H, H_2-3'), 0.93 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (100 MHz, MeOD) δ 83.4 (C-6'), 80.3 (C-3), 73.1 (C-5'), 71.3 (C-4), 70.2 (C-2), 68.2 (C-5), 58.6 (C-6), 56.3 (C-1), 54.8 (C-1'), 33.8 (C-7'), 31.3 (C-4'), 28.0 (C-8',C-9',C-10'), 25.8 (C-3'), 25.4 (C-2'). $[\alpha]^{20}_{D}$ = +7.2 (c = 1, MeOH). IR/cm^{-1}: 3280, 2951, 2862, 1734, 1637, 1458, 1387, 1362, 1113, 1032. HRMS: found 320.24339 $[C_{16}H_{33}NO_5+H]^+$, calculated for $[C_{16}H_{33}NO_5+H]^+$ 320.24315.

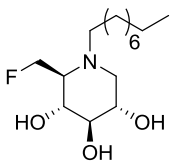
C-6 fluorinated DNJ derivatives

N-Butyl-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (177):



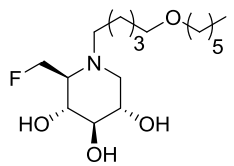
1-Bromobutane (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **177.** ^{1}H NMR (400 MHz, MeOD) δ 5.04 (qd, *J* = 12.0, 2.4 Hz, 1H, H-6a), 4.92 – 4.88 (m, 1H, H-6b), 3.74 (td, *J* = 10.6, 10.1, 4.7 Hz, 1H, H-2), 3.65 – 3.56 (m, 1H, H-4), 3.54 (dd, *J* = 12.2, 4.8 Hz, 1H, H-1a), 3.44 (t, *J* = 9.2 Hz, 1H, H-3), 3.41 – 3.32 (m, 2H, H-1'a, H-5), 3.23 (td, *J* = 12.2, 5.2 Hz, 1H, H-1'b), 3.04 (t, *J* = 11.6 Hz, 1H, H-1b), 1.81 – 1.66 (m, 2H, H_2-2'), 1.48 – 1.40 (m, 2H, H_2-3'), 1.00 (t, *J* = 7.4 Hz, 3H, H_3-4'). ^{13}C NMR (100 MHz, MeOD) δ 78.6 (d, J_{CF} = 170.0 Hz, C-6), 77.0 (C-3), 68.5 (C-4), 67.7 (C-2), 66.4 (d, J_{CF} = 17.7 Hz, C-5), 55.1 (C-1), 54.6 (C-1'), 26.2 (C-2'), 20.8 (C-3'), 13.8 (C-4'). IR/cm^{-1}: 3208, 2909, 1663, 1437, 1184, 1132, 1055, 1024. HRMS: found 222.14995 $[C_{10}H_{20}FNO_3+H]^+$, calculated for $[C_{10}H_{20}FNO_3+H]^+$ 222.15000.

N-Nonyl-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (178):



1-Bromononane (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **178**. ^{1}H NMR (400 MHz, MeOD) δ 5.05 (ddd, *J* = 12.8, 12.3, 2.4 Hz, 1H, H-6a), 4.97 – 4.90 (m, 1H, H-6b), 3.72 (ddd, *J* = 10.5, 10.0, 4.7 Hz, 1H, H-2), 3.59 (t, *J* = 9.5 Hz, 1H, H-4), 3.52 (dd, *J* = 12.2, 4.8 Hz, 1H, H-1a), 3.43 (t, *J* = 8.9 Hz, 1H, H-3), 3.40 – 3.34 (m, 2H, H-1'a, H-5), 3.21 (td, *J* = 12.4, 5.4 Hz, 1H, H-1'b), 3.03 (t, *J* = 11.6 Hz, 1H, H-1b), 1.80 – 1.70 (m, 2H, H_2-2'), 1.47 – 1.19 (m, 12H, H_2-3', H_2-4', H_2-5', H_2-6', H_2-7', H_2-8'), 0.90 (t, *J* = 6.6 Hz, 3H, H_3-9'). ^{13}C NMR (100 MHz, MeOD) δ 78.6 (d, J_{CF} = 168.8 Hz, C-6), 77.1 (C-3), 68.6, 68.5 (C-4), 67.8 (C-2), 66.4 (d, J_{CF} = 17.8 Hz, C-5), 54.8 (C-1), 54.4 (C-1'), 32.9, 30.4, 30.2, 30.2, 27.6, 24.3, 23.6 (C-2' – C-8'), 14.4 (C-9'). IR/cm^{-1}: 3244, 2926, 2857, 1666, 1456, 1435, 1200, 1184, 1086, 1022. HRMS: found 292.22803 $[C_{15}H_{30}FNO_3+H]^+$, calculated for $[C_{15}H_{30}FNO_3+H]^+$ 292.22825.

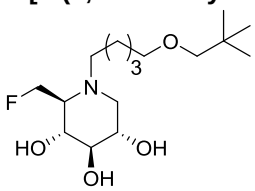
N-[5-(Hexyloxy)pentyl]-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (179):



Pentyloxyhexyl bromide (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **179**. ^{1}H NMR (400 MHz, MeOD) δ 5.11 – 4.89 (m, 2H, H_2-6), 3.70 (ddd, *J* = 14.4, 8.6, 4.4 Hz, 1H, H-2), 3.58 (t, *J* = 9.9 Hz, 1H, H-

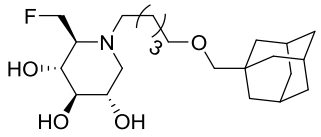
4), 3.50 (dd, *J* = 12.2, 4.8 Hz, 1H, H-1a), 3.46 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.43 (t, *J* = 6.6 Hz, 2H, H_2-6'), 3.41 – 3.29 (m, 3H, H-3, H-1'a, H-5), 3.21 (td, *J* = 12.2, 5.1 Hz, 1H, H-1'b), 3.00 (t, *J* = 11.5 Hz, 1H, H-1b), 1.84 – 1.74 (m, 2H, H_2-2'), 1.69 – 1.60 (m, 2H, H_2-4'), 1.58 – 1.53 (m, 2H, H_2-7'), 1.48 – 1.45 (m, 2H, H_2-3'), 1.40 – 1.23 (m, 6H, H_2-8', H_2-9', H_2-10'), 0.93 (t, *J* = 7.0 Hz, 3H, H_3-11'). ^{13}C NMR (100 MHz, MeOD) δ 78.6 (d, J_{CF} = 174.4 Hz, C-6), 72.1 (C-6'), 71.4 (C-5'), 68.7 (C-4), 67.9 (C-2), 66.4 (d, J_{CF} = 17.7 Hz, C-5), 54.7 (C-1), 54.6 (C-1'), 32.8, 30.7, 30.1, 26.9, 24.4, 24.2, 23.6 (C-2' – C-4', C-7' – C-10'), 14.4 (C-11'). IR/cm^{-1}: 3310, 2934, 2860, 2800, 1670, 1456, 1435, 1377, 1204, 1134, 1022, 839, 800, 723. HRMS: found 336.25416 $[C_{17}H_{34}FNO_4+H]^+$, calculated for $[C_{17}H_{34}FNO_4+H]^+$ 336.25446.

N-[5-(3,3-Dimethyl-1-propyloxy)pentyl]-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (180):



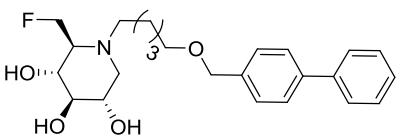
1-Bromo-5-(2,2-dimethyl-1-propoxy) pentane (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **180**. ^{1}H NMR (400 MHz, MeOD) δ 5.11 – 4.86 (m, 2H, H_2-6), 3.71 (td, *J* = 10.5, 4.7 Hz, 1H, H-2), 3.59 (t, *J* = 9.2 Hz, 1H, H-4), 3.52 (dd, *J* = 12.2, 4.8 Hz, 1H, H-1a), 3.45 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.43 – 3.34 (m, 3H, H-1'a, H-3, H-5), 3.23 (ddd, *J* = 12.7, 12.3, 5.2 Hz, 1H, H-1b), 3.08 (s, 2H, H_2-6'), 3.03 (t, *J* = 11.6 Hz, 1H, H-1b), 1.90 – 1.70 (m, 2H, H_2-2'), 1.65 (dt, *J* = 8.0, 6.4 Hz, 2H, H_2-4'), 1.54 – 1.36 (m, 2H, H_2-3'), 0.90 (s, 9H, H_3-8', H_3-9', H_3-10'). ^{13}C NMR (100 MHz, MeOD) δ 82.5 (C-6'), 78.48 (d, J_{CF} = 174.2 Hz, C-6) 78.1 (C-3), 72.0 (C-5'), 68.6 (C-4), 67.8 (C-2), 66.38 (d, J_{CF} = 17.8 Hz, C-5), 54.8 (C-1), 54.7 (C-1'), 32.9 (C-7'), 30.1 (C-4'), 27.1 (C-8', 9', 10'), 24.9 (C-3'), 24.4 (C-2'). IR/cm^{-1}: 3302, 2955, 2866, 1670, 1435, 1387, 1364, 1204, 1136, 1026. HRMS: found 322.23860 $[C_{16}H_{32}FNO_4+H]^+$, calculated for $[C_{16}H_{32}FNO_4+H]^+$ 322.23881.

N-[5-(Adamantan-1-yl-methoxy)pentyl]-6-fluoro-1,5-imino-D-glucitol (181):



5-(Adamantan-1-yl-methoxy)pentyl bromide (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **181.** ^{1}H NMR (400 MHz, MeOD) δ 3.70 (td, *J* = 10.5, 4.7 Hz, 1H, H-2), 3.54 (t, *J* = 9.5 Hz, 1H, H-4), 3.44 (dd, *J* = 12.4, 5.0 Hz, 1H, H-1a), 3.39 (t, *J* = 9.1 Hz, 1H, H-3), 3.31 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.33 – 3.20 (m, 2H, H-5, H-1'a), 3.13 (ddd, *J* = 12.8, 12.3, 5.3 Hz, 1H, H-1'b), 2.93 (t, *J* = 11.6 Hz, 1H, H-1b), 2.88 (s, 2H, H_2-6'), 1.85 (t, *J* = 3.4 Hz, 3H, 3 x CH ada), 1.76 – 1.63 (m, 2H, H_2-2'), 1.65 – 1.52 (m, 8H, 3 x CH_2 ada, H_2-4'), 1.44 (d, *J* = 3.0 Hz, 6H, 3 x CH_2 ada), 1.41 – 1.23 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 82.7 (C-6'), 78.6 (d, J_{CF} = 170.7 Hz, C-6), 77.0 (C-3), 71.7 (C-5'), 68.1 (C-4), 67.1 (C-2), 65.97 (d, J_{CF} = 17.8 Hz, C-5), 54.5 (C-1), 54.5 (C-1'), 40.4 (CH_2 ada), 37.9 (CH_2 ada), 34.8 (C_q ada), 29.6 (C-4'), 29.2 (CH ada), 24.0 (C-3'), 23.6 (C-2'). IR/cm^{-1}: 3354, 2901, 2847, 2590, 1651, 1446, 1205, 1184, 1140, 1018. HRMS: found 400.28468 $[C_{22}H_{38}FNO_4+H]^+$, calculated for $[C_{22}H_{38}FNO_4+H]^+$ 400.28576.

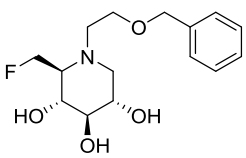
N-[(Biphenyl-4-yl-methoxy)pentyl]-6-fluoro-1,5-imino-D-glucitol (182):



(Biphenyl-4-yl-methoxy)-pentyl bromide (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **182**. ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 7.9 Hz, 4H, H_{Ar} BiPh), 7.47 – 7.31 (m, 5H, H_{Ar} BiPh), 5.12 – 4.75 (m, 2H, H_2-6), 4.55 (s, 2H, H_2-6'), 3.70 (td, *J* = 10.0, 4.5 Hz, 1H, H-2), 3.57 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.51 (dd, *J* = 12.2, 4.9 Hz, 1H, H-4), 3.45 – 3.30 (m, 3H, H-1a, H-3, H-1'a), 3.23 (ddd, *J* = 13.1, 12.5, 5.7 Hz, 1H, H-1'b), 3.02 (t, *J* = 11.6 Hz, 1H, H-1b), 1.89 – 1.75 (m, 2H, H_2-2'), 1.76 – 1.66 (m, 2H, H_2-4'), 1.61 – 1.44 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 142.0, 138.7 (C_q BiPh), 129.9 – 127.9 (C_{Ar} BiPh), 78.4 (d, J_{CF} = 169.5 Hz, C-6), 77.9 (C-3), 73.7 (C-6'), 71.0 (C-5'), 68.5 (C-4), 67.8 (C-2), 66.3 (d, J_{CF} = 17.7 Hz, C-5), 54.9 (C-1), 54.7 (C-1'), 30.0 (C-4'), 24.5 (C-3'), 24.0 (C-2'). IR/cm^{-1}:

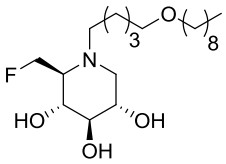
3304, 2918, 2864, 1672, 1487, 1435, 1364, 1203, 1134, 1022, 841. HRMS: found 418.23818 $[C_{24}H_{32}FNO_4+H]^+$, calculated for $[C_{24}H_{32}FNO_4+H]^+$ 418.23881.

_N_-(Benzyloxy)ethyl-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (183):



(2-Benzyloxy)ethyl bromide (0.375 mmol) was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **183**. ^{1}H NMR (400 MHz, MeOD) δ 7.38 – 7.25 (m, 5H, H_{Ar} Bn), 5.25 – 4.90 (m, 2H, H_2-6), 4.59 (s, 2H, CH_2 Bn), 3.85 (t, *J* = 4.9 Hz, 2H, H_2-2'), 3.78 – 3.61 (m, 2H, H-2, H-1'a), 3.60 – 3.55 (m, 2H, H-4, H-1a), 3.49 (dt, *J* = 14.1, 4.9 Hz, 1H, H-1'b), 3.39 (t, *J* = 9.0 Hz, 1H, H-3), 3.05 (t, *J* = 11.6 Hz, 1H, H-1b). ^{13}C NMR (100 MHz, MeOD) δ 138.5 (C_q Bn), 129.6 – 129.2 (CH_{Ar} Bn), 78.8 (d, J_{CF} = 169.1 Hz, C-6), 74.4 (C-3'), 68.5 (C-4), 67.8 (C-2), 66.2 (d, J_{CF} = 17.6 Hz, C-5), 64.6 (C-2'), 55.6 (C-1), 54.2 (C-1'). IR/cm^{-1}: 3235, 2874, 1670, 1456, 1437, 1364, 1202, 1134, 1026. HRMS: found 300.16042 $[C_{15}H_{22}FNO_4+H]^+$, calculated for $[C_{15}H_{22}FNO_4+H]^+$ 300.16056.

_N_-(Nonyloxy)pentyl-1,6-dideoxy-6-fluoro-1,5-imino-D-glucitol (184):



Pentyloxynonyl bromide was subjected to general procedure A with 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol (0.25 mmol) to provide **184**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 5.05 (ddd, *J* = 11.0, 10.2, 2.3 Hz, 1H, H-6a), 4.99 – 4.92 (m, 1H, H-6b), 3.71 (ddd, *J* = 10.9, 9.0, 4.8 Hz, 1H, H-2), 3.59 (t, *J* = 9.6 Hz, 1H, H-4), 3.52 (dd, *J* = 12.2, 4.8 Hz, 1H, H-1a), 3.46 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.43 (t, *J* = 6.5 Hz, 2H, H_2-6'), 3.40 – 3.30 (m, 3H, H-3, H-1'a, H-5), 3.22 (ddd, *J* = 12.7, 12.3, 5.2 Hz, 1H, H-1'b), 3.02 (t, *J* = 11.6 Hz, 1H, H-1b), 1.89 – 1.69 (m, 2H, H_2-2'), 1.73 – 1.62 (m, 2H, H_2-4'), 1.63 – 1.53 (m, 2H, H_2-7'), 1.53 – 1.42 (m, 2H, H_2-3'), 1.38 – 1.23 (m, 12H, H_2-8', H_2-9', H_2-10', H_2-11', H_2-12', H_2-13'), 0.90 (t, *J* = 6.8 Hz, 3H, H_2-14'). ^{13}C NMR (100 MHz, MeOD) δ 78.6 (d, *J* = 168.3 Hz, C-6), 72.1 (C-6'), 71.4 (C-5'), 77.2 (C-3), 68.6 (C-4), 67.8 (C-2), 66.4 (d, *J* = 17.7 Hz, C-5), 55.1 (C-1), 54.7 (C-1'), 33.0, 30.7, 30.6, 30.4, 30.1, 27.2, 24.4, 24.1, 23.7 (C-2' – C-4', C-7' – C-13'), 14.4 (C-14'). IR/cm^{-1}: 3294, 2926, 2855, 1670, 1458, 1437, 1202, 1132, 1022. HRMS: found 378.30158 $[C_{20}H_{40}FNO_4+H]^+$, calculated for $[C_{20}H_{40}FNO_4+H]^+$ 378.30141.

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Chinese Summary 中文小结

本书对亚胺糖（iminosugar）及其衍生化合物作为糖代谢相关酶抑制剂的设计、合成与生物评价进行了分析研究。首先选用 1-脱氧野尻霉素（1-deoxynojirimycin, DNJ）及其已知的 N-烷基化衍生物，对其哌啶环结构和（或）N 端取代基进行了修改或修饰。然后使用葡糖神经酰胺（glucosylceramide）代谢相关酶对修饰后的亚胺糖衍生物的生物活性进行评价。其中，葡糖神经酰胺（glucosylceramide）代谢相关酶包括葡糖神经酰胺合成酶（glucosylceramide synthase, GCS、溶酶体葡糖神经酰胺酶（lysosomal glucosylceramidase, GBA1）和中性葡萄糖神经酰胺酶（neutral glucosylceramidase, GBA2。最后，对所有新化合物与已知化合物的抑制效力进行了比较与评价。

第 1 章介绍了亚胺糖在生物医学中目前的应用及其应用潜力。

鉴于亚胺糖拥有重要的生物活性和药物潜力，且天然丰度低，难以从自然中大量获得，在过去几十年，研究人员对亚胺糖的不同合成策略进行了研究与报道。**第 2 章**回顾了一些 DNJ 分子的合成策略，着重讨论了双还原胺化（double reductive amination）在合成过程中发挥的关键作用。本论文中提出的几个合成路线都以其作为关键步骤。

与单糖 DNJ 相比，目前其糖基化衍生物尚未受到明显关注。**第 3 章**阐述了从相应二糖开始合成糖基化 DNJ 衍生物的有效策略，并成功地合成了五种不同的糖基化 DNJ 衍生物。合成路线的关键在于：选择性地暴露原料二糖的还原性葡萄糖的异头中心，并将其还原为二醇，氧化为 5-酮醛，然后进行双还原胺化。

GBA2 选择性抑制剂不仅是研究 GBA2 生物功能的理想工具分子，还是潜在的临床候选药物。研究认为 GBA2 与溶酶体贮积症（lysosomal storage disorders，高雪氏病（Gaucher disease）和 C 型尼曼氏病（Niemann-Pick type C disease）密切相关。**第 4 章**关注了 N-烷基化 DNJ 衍生物的设计和合成，构建了由 N-戊氧基新戊基异构体亚胺糖组成的化合物库，并对其作为 GBA2 选择性抑制剂的生物活性进行了评价。

具有 GCS/GBA2 双重抑制活性的亚胺糖作为溶酶体贮积症的药物开发候选分子拥有巨大的潜力。**第 5 章**中设计了 16 种 *N*-烷基修饰的 DNJ 和 L-艾杜糖构型的 DNJ 衍生物，并评价了其作为 GCS/GBA2 双重抑制剂的效果。遗憾的是，在此化合物库中并未发现更出色的新抑制剂。

第 6 章设计了四个构型异构的双羟甲基亚胺糖的合成途径。使用了不同的脂肪链对这些特殊的亚胺糖进行修饰，从而构成了拥有 36 个新型化合物的化合物库。分析此化合物库中的化合物对葡糖神经酰胺代谢酶（GCS，GBA1 和 GBA2）的抑制作用发现，额外的羟甲基（与本论文前述的母体亚氨基糖 DNJ 及其异构体相比）未带来相应的抑制效力，对不同的靶酶也没有增加选择性。

第 7 章归纳和总结了本论文的研究成果，并对未来的研究工作进行了展望。提出了新的亚胺糖衍生物 C-5 氧杂环丁烷亚胺糖的合成路线。初步评估了亚胺糖 C-2 和 C-3 结构对于其作为 GCS 抑制剂活性的重要性：（2*S*,3*R*）立体构型可能是亚胺糖拥有 GCS 抑制活性的必要条件。此外，通过分析氟原子取代 6 号位羟基对 DNJ 活性的影响，结果表明引入电负性更高的氟原子并未提高 DNJ 的活性。

List of Publications

1. Lahav, D.; Liu, B.(Joint first author); van den Berg, R.J.B.H.N.; van den Nieuwendijk, A.M.C.H.; Wennekes, T.; Ghisaidoobe, A.; Breen, I.; Ferraz, M.; Kuo, C. L.; Wu, L.; Geurink, P.; Ovaa, H.; van der Marel, G.; van der Stelt, M.; Boot, R.; Davies, G.; Aerts, J.; Overkleeft, H. A fluorescence polarization activity-based protein profiling assay in the discovery of potent, selective inhibitors for human non-lysosomal glucosylceramidase. *JACS*. accepted 22 Sept. **2017.**

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5. Cao, S.; Cheng, B. Z.; Liu, B.; He, X. Effect of mixed metal tanning using zinc and titanium with suitable masking agents. *J. Soc. Leath. Tech. Chem*. **2015**, *99*, 120-123.

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Curriculum Vitae

Bing Liu was born on January 13th 1989 in Puyang, Henan, China. During her High School years, she got interested in Chemistry. After the College Entry Examinations, she enrolled at the College of Chemistry and Material Science at Shandong Agricultural University. Here she obtained her Bachelor's Degree in Applied Chemistry. During this time she also took on English Literature as a second major, which resulted in another Bachelor's Degree obtained in 2009.

After completing her bachelor studies, she entered the College of Life Science at Beijing Normal University. Here she followed a major in Biochemistry and Molecular Biology. She obtained her Master's Degree in 2012, under the supervision of Prof. Xiang Benqiong and Prof. Wei Qun.

Following this she applied for a PhD study at Leiden University in 2012. In December of that year she started her study in the Bio-Organic Synthesis Group under the supervision of Prof. Dr. Herman S. Overkleeft and Dr. Richard J. B. H. N. van den Berg. She was awarded a scholarship by the CSC (China Scholarship Council) in 2013, which lasted until 2016. Her PhD study was focussed on the iminosugars as inhibitors for glucosylceramide processing enzymes. Her research consisted of the synthesis and the evaluation of the activity of various iminosugar compound libraries.